

EFFECTS OF HISTAMINE  
AND PENTAGASTRIN ON FASTING EQUINE  
GASTRIC AND DUODENAL CONTENTS

By

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by

Diane Lynn Kitchen

This dissertation is dedicated to my father, Hiram Kitchen, D.V.M., Ph.D., who taught me the importance of the pursuit of excellence. I continuously strive to approach the high standards he spent a lifetime instilling in me. Even today, I look to his approval as the ultimate in reward. Thank you, Daddy, and I do wish you were here to share this with me.

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The composition of equine gastric contents has been determined to differ markedly from that of other monogastric species. In the fasted animal, there is a voluminous sodium-rich fluid component which becomes greater during pentagastrin infusion, which is not eliminated by acid blockade. Potential pancreatic stimulation by pentagastrin was suggested by Alexander and Hickson. Histamine infusion, however, seemed to cause a classic parietal secretion, as opposed to the mixed parietal and nonparietal response to pentagastrin. These findings led to the formulation of the hypothesis for this dissertation: *In the equine gastric*

*cannula model, the vigorous sodium-rich component of pentagastrin stimulated gastric contents is extragastric in origin.*

The testing of this hypothesis was accomplished by a series of studies on horses with chronic gastric cannulae. A full histamine dose-response study was necessary to determine an optimal dose for the stimulation of maximal acid output. Since this required pretreatment of the horses with the H-1 receptor antagonist, pyrilamine maleate, a small study of the effect of this pretreatment on pentagastrin-stimulated secretion was designed. A technique was developed for the placement of an intraduodenal ballooned catheter via the gastric cannula to occlude the pylorus. A study was also performed to evaluate the effect of the presence of the intraduodenal catheter. Finally, the critical study involving a comparison of the gastric and duodenal contents during histamine and pentagastrin infusion, with and without obstruction of the pylorus, was done.

Gastric contents were analyzed in each of the studies for volume and electrolyte composition. The histamine-induced maximal acid output was equivalent to that previously

reported for horses stimulated with pentagastrin.

Pyrilamine maleate dampened the gastric acid secretory response to pentagastrin infusion. The introduction of an intraduodenal catheter did not alter the maximal acid output to pentagastrin, although it may have enhanced the reflux of duodenal fluid into the gastric lumen. Most importantly, the obstruction of the pylorus with the balloon catheter significantly decreased the sodium output in gastric collections suggesting that the vigorous sodium-rich component of pentagastrin stimulated secretion is primarily of extragastric origin.

CHAPTER 1  
INTRODUCTION AND REVIEW OF LITERATURE

Introduction

The regulation of gastric secretion has long interested scientists and clinicians due to the vital role gastric acid secretion plays in the normal gastrointestinal function and in certain pathologic conditions. The stomach, with both endocrine and exocrine function, is not a simple collection vat for food prior to digestion. A diverse group of cells with numerous capabilities are found within the highly specialized gastric mucosa.<sup>1</sup> Parietal cells secrete acid at the apical membranes containing the H<sup>+</sup>/K<sup>+</sup> ATPase pump.<sup>2</sup> Other cells are responsible for the production of mucus, zymogens, and other biologically active peptides and amines.<sup>1</sup> Numerous endocrine cells secrete substances that modulate various gastrointestinal functions.<sup>1</sup> The secretion of hydrochloric acid by the parietal cells is regulated by neural, hormonal, and paracrine mechanisms which interact to

control the rate of secretion.<sup>1-3</sup> Acetylcholine is the primary neurotransmitter involved in gastric acid secretion. Muscarinic nerve endings near the gastric glands release acetylcholine as part of the vagal reflex system.<sup>3</sup> Enteric neurons in Meissner's plexus release GRP (gastrin releasing peptide) which acts on G cells in the gastric antrum. Gastrin is the peptide hormone released in response to specific substrates within the gastric lumen and distension of the antrum. Released by antral G cells, gastrin is an important hormone which is involved in all phases of gastric secretion and also exerts influence on DNA transcription and cellular replication.<sup>1</sup> Histamine acts directly on parietal cells, as a paracrine substance, to stimulate gastric acid secretion via H-2 receptors. Histamine originates from enterochromaffin-like (ECL) cells present within the mucosa, in response primarily to gastrin stimulation, with modulation by numerous other substances.<sup>1</sup>

### Historical Background

Understanding the mechanisms of gastric acid secretion and the regulation of these mechanisms has required decades

of research by many eminent scientists using a wide array of models and techniques. From the time of Pavlov and the fistulated dogs until the "in vitro" cellular studies of Håkanson et al., debate has raged around the regulation of gastric acid secretion. Pavlov's work with fistulated models confirmed that subjective observations of a link between emotional status and digestive function were correct and introduced the role of a central neural component of gastric secretory regulation.<sup>4</sup> Even today we use the term "Pavlovian" when referring to the brain's input into a function, such as the cephalic phase of gastric secretion.

Bayliss and Starling paved the way to investigation of hormonal substances involved in gastrointestinal secretion.<sup>5</sup> In 1906, Edkins suggested that a hormone "gastrin" was released in the pyloric portion of the stomach and resulted in the gastric phase of the acid secretory response.<sup>6</sup> The presence of this distinct secretagogue was demonstrated by Komarov in 1938,<sup>7</sup> and clarified in 1941 by Gregory and Ivy.<sup>8</sup> Gregory and Tracy were able to isolate the substance in two forms from pig antral mucosa and validate the hormonal regulation of gastric secretion by gastrin in the 1960s.<sup>9</sup>

Histamine was reported to stimulate the secretion of gastric acid in the early 1920s. Then, in the late 1930s, MacIntosh stated that vagal stimulation resulted in histamine release within the gastric mucosa<sup>10</sup>; however, controversy surrounded the role of histamine since known antihistamine agents were unable to prevent acid secretion.<sup>11</sup> The identification of different subtypes of histamine receptors by Black et al. in the 1970s and subsequent studies with H-2 receptor antagonist clearly demonstrated that histamine was an integral component in the normal gastric secretory response.<sup>11,12</sup> The complex interworking of each of these components confused investigators and resulted in conflicting studies. Only in the 1970s, with studies focusing on "in vitro" cellular preparations and technical advances in immunology and histology, were scientists able to begin unravelling this complex regulatory process. The enterochromaffin-like (ECL) cell was the key to the combined action of acetylcholine, gastrin, histamine and many other effectors.<sup>1</sup> Though ECL cells had been noticed in the early drawings and writings of Heidenhain, their role in the secretory response was not known.<sup>1</sup> The demonstration by Håkanson et al.<sup>13</sup> and Capella

et al.<sup>14</sup> that the fundic ECL cells contained histamine, began the explosion of new concepts in gastric secretory regulation which has led to better understanding of the process.

### Review of Literature

Today, it is apparent that gastric acid secretion by parietal cells results from paracrine histamine released by nearby ECL cells. The release of histamine is mediated by many substances including gastrin, acetylcholine, somatostatin, vasoactive intestinal peptide (VIP), prostaglandins, calcitonin gene-related peptide, TGF- $\alpha$ , and even histamine.<sup>1</sup> Histamine acts on the basolateral membrane of parietal cells at H-2 receptors.<sup>2,3</sup> Stimulation of these receptors activates the basolateral adenylate cyclase and leads to increased intracellular cAMP within the parietal cell.<sup>15</sup> In contrast, parietal cell gastrin receptors and muscarinic M3 receptors result in increased intracellular Ca<sup>++</sup> when stimulated.<sup>16</sup> The increased cAMP and/or Ca<sup>++</sup> may activate protein kinases involved in the phosphorylation of the apical H,K ATPase as occurs in Na,K ATPases.<sup>16</sup> Several

cellular changes occur with activation of the secondary messenger system within the parietal cell. The proton pump, H,K ATPase, is present in the membrane of cytoplasmic membrane compartments during the resting or unstimulated state and, after stimulation, within the membranes of extensive apical canaliculi.<sup>16</sup> The mechanics of this transformation are not clearly understood. It is possible that the cytoplasmic vesicles observed in the resting state are connected to the apical membrane and that tubules simply expand to expose the proton pump to the lumen of the gastric glands. An alternative explanation is that activation of the cell results in the fusion of cytoplasmic membranes with the apical membrane.<sup>16</sup>

Another change occurring following stimulation of the parietal cell is the activation and transformation of parallel K and Cl channels, which provide the extracellular K<sup>+</sup> needed for the proton pump.<sup>16</sup> The pump requires oxygen as well as Mg<sup>++</sup>. The energy required by the proton pumps is supplied as ATP by the large mitochondrial content in the parietal cell.<sup>16</sup> The proton pump transports H<sup>+</sup> into the gastric gland in exchange for K<sup>+</sup>. In order to maintain intracellular homeostasis, several membrane exchange

pathways are present within the membrane of the parietal cell including  $\text{Cl}/\text{HCO}_3$  and  $\text{Na}/\text{H}$  exchangers.<sup>15</sup> During stimulation, the parietal cell secretes  $\text{H}^+$  actively via the proton pump,  $\text{Cl}^-$  passively via the  $\text{Cl}$  channel, and  $\text{H}_2\text{O}$  passively into the gastric lumen.<sup>15</sup> Parietal secretion of  $\text{HCl}$  provides a high concentration ( $\sim 140$  mEq/L) of acid within the gastric glands that empty into the lumen of the stomach.

Gastric secretion is commonly described as either basal or stimulated. Basal secretion is also termed interdigestive secretion and occurs without external stimulation, such as ingestion of food, or conditioned response.<sup>2,17</sup> In terms of volume and acid content, basal secretion varies greatly between species.<sup>17</sup> A circadian rhythm has been observed in human basal secretion with higher rates during the evening and low rates in the morning.<sup>2,3,17,18</sup> The rate of basal secretion is independent of serum gastrin concentration and is not abolished by vagotomy.<sup>2,17</sup>

Stimulated gastric secretion is classically divided into three phases, with some overlap between them. These phases are commonly termed cephalic, gastric, and

intestinal.<sup>2,3,17,18</sup> The link between the brain and gastric function has been speculated about since the early 1800's.<sup>19</sup> Sight, smell, taste, thought, and swallowing stimulate gastric acid secretion during the cephalic phase.<sup>2,3,9,10</sup> The vagus nerve is the key link in the cephalic phase through its stimulation of gastrin release as well as direct innervation of the parietal cell.<sup>2,17,18</sup> As mentioned, these effects may be mediated through ECL cells rather than directly through receptors on the parietal cell. Many neurotransmitters and certain peptides have been shown to act centrally on the regulation of acid secretion.<sup>19</sup> Cholinergic agonists, prostaglandin inhibitors, GABAergic agonists, gastrin/CCK, TRH-related peptides, and somatostatin-related peptides administered into the CSF stimulate gastric acid secretion. Inhibition occurs following CSF injection of cholinergic antagonists, adrenergic agonists, prostaglandins, serotonin, bombesin-like peptides, opioid peptides, CRF-like peptides, and calcitonin-related peptides.<sup>19</sup>

The gastric phase of stimulated secretory response is a result of gastric distension or chemical stimulation of the gastric mucosa.<sup>2,3,17,18</sup> This phase is mediated primarily

by gastrin. Distension of the stomach walls activates stretch receptors involved in release of gastrin. However, this release does not occur if the gastric contents are acidic due to a pH-sensitive, oxyntopyloric reflex with inhibition by somatostatin.<sup>2,17,18</sup> Certain breakdown products of food are strong stimulants of gastric acid secretion, particularly peptides and amino acids, specifically, phenylalanine and tryptophan.<sup>2,17,18</sup> These stimulants induce the release of gastrin by action at the apical microvilli of G cells within the antral mucosa.<sup>17</sup>

The intestinal phase of acid secretion is responsible for only a small portion of the total acid secretory response.<sup>18</sup> Stimulating agents are the same as those involved in the gastric phase. The substances act directly at G cells in the upper small intestine as a gastrin-dependent mechanism and absorbed amino acids exert their effect by a gastrin-independent mechanism.<sup>18</sup> All phases of acid secretion are, in part, mediated by gastrin, through the release of histamine from ECL cells.<sup>1</sup>

The secretion of gastric acid follows the action of histamine on H-2 receptors on the parietal cell. Inhibition of histamine release allows the parietal cell to return to a

resting state. Acidification of the gastric contents inhibits gastrin release by release of somatostatin from antral D cells.<sup>18</sup> The presence of acid, fat, or hyperosmolar solutions within the small intestine inhibits the acid secretory response through one or more of the peptides such as secretin, peptide YY, neurotensin, VIP (vasoactive intestinal peptide), GIP (gastric inhibitory peptide), and enteroglucagon released by cells within the small intestinal mucosa.<sup>17,18</sup> These inhibitory substances have receptors on the ECL cell and have been shown to inhibit the release of histamine from these cells.<sup>1</sup> Histamine also exerts negative feedback on ECL cells via H-1 and H-3 receptors.<sup>1</sup> The rapid catabolism of histamine and its speedy removal from the extracellular space surrounding the parietal cell eliminates the stimulation of these cells and terminates the secretory process.<sup>20</sup>

Many drugs have demonstrated antisecretory actions that have been crucial in clarifying the mechanisms of acid secretion and in treatment of pathologic conditions related the secretion of gastric acid.<sup>21</sup> Histamine H-2 receptor antagonists are able to prevent gastrin, food, and vagal-induced acid secretion. This finding was pivotal in the

determination of the central role of histamine in the secretory response.<sup>22</sup> As a result, numerous H-2 blockers have become a mainstay in the treatment of peptic ulcers.<sup>21</sup> Substituted benzimidazoles, such as omeprazole, have more recently joined the battery of antiulcer medication due to their inhibition of the H,K ATPase.<sup>21</sup> Certain prostaglandin E<sub>2</sub> analogues also have an antisecretory effect, due to actions at CNS as well as ECL cell level.<sup>1,21</sup> Gastrin receptor antagonists (ie. Proglumide) are also capable of inhibiting acid secretion.<sup>21</sup> The target of some presently available drugs and many of the drugs of the future may not be parietal cells directly, but other cells within the gastric mucosa which act on the parietal cell.<sup>23</sup> Accordingly, the increasing understanding of the role of the ECL cell is likely to make it the target of investigational agents for the regulation of acid secretion.

The gastric ECL cell is considered to be one of the amine precursor uptake decarboxylation (APUD) series of cells.<sup>1,24</sup> Numerous endocrine cells are found scattered within the gastric mucosa and may represent from 0.5% to 2% of the cells present. The prevalence of ECL cells vary among species, as they are particularly common in the rat

and appear in lesser numbers in the dog and primates.<sup>1,24</sup> Other endocrine cells observed in the gastric mucosa include enterochromaffin cells which produce 5-hydroxytryptamine (serotonin), D cells that secrete somatostatin, gastrin-producing G cells, and P and X cells which have unknown functions.<sup>1</sup> The ECL cells are found near parietal cells within the gastric glands and have prominent cytoplasmic extensions.<sup>1,24</sup> They contain a large number of cytoplasmic vesicles and electron-dense granules, and take up aromatic amino acids and decarboxylate them. Histidine decarboxylase (HDC) and histamine are also found within these cells.<sup>1,24</sup> Histamine is concentrated into cytoplasmic vesicles by a V-type ATPase which acts as a H<sup>+</sup>/histamine antiporter.<sup>1,22,24</sup> As indicated above, the production and storage of histamine by the ECL cell makes it the critical interface in the regulation of gastric acid secretion.<sup>1,24</sup> The primary mediator of histamine release is gastrin acting through the CCK-B receptor to increase cytosolic Ca<sup>++</sup>.<sup>1,22,24</sup> Histamine release can also be stimulated by acetylcholine at muscarinic M1 receptors, epinephrine through  $\beta$  adrenergic receptors, isoproterenol, forskolin, interleukin 1 $\beta$  and VIP,

and can be inhibited by somatostatin (subtype 2), TGF- $\alpha$ , TGF- $\beta$ , calcitonin gene-related peptide, and histamine via H-1 and H-3 receptors.<sup>1,22,24,25</sup> It appears that there is substantial neurotransmitter modulation of gastrin and its regulation of histamine release from ECL cells.<sup>25</sup> Although, it is known that Ca<sup>++</sup> acts as a secondary messenger within the ECL cell, cAMP is likely to also play a role in the release of histamine.<sup>1,22,24</sup>

In addition to stimulating the release of histamine, gastrin regulates HDC activity and ECL cell proliferation.<sup>1,24</sup> It stimulates DNA synthesis by a pathway distinct from that of histamine release, although both processes appears to begin with the binding of gastrin at the CCK-B receptors.<sup>1,24</sup> Hypergastrinemia has been associated with increased numbers of ECL cells and may play a significant part in the development of gastric carcinoids.<sup>1,24</sup> The chronic use of antiulcer medication with resultant hypergastrinemia have been shown to lead to ECL hyperplasia and gastric mucosal hypertrophy.<sup>1,22,24</sup> The recent advances in the "in vitro" cellular techniques have expanded our knowledge of the regulation of the gastric secretory response; however, as history shows us, advances

just open the door to a multitude of additional questions. Although, much knowledge has been gained by isolated cell work such as that with the ECL cell, the wide array of species differences points to the continuing need for both "in vivo" and "in vitro" studies.

Early classical studies were "in vivo," performed primarily on animals with a variety of surgically prepared pouches or fistulas. Even human studies in the early 1900's, were performed on subjects with gastric fistulas.<sup>19</sup> Historically, experimental preps commonly utilized dogs and cats with transplanted pouches or surgically isolated stomachs.<sup>8,26,27</sup> Over time, chronic gastric cannulas have been placed in the stomachs of dogs, rats, rabbits, pigs, cats, humans, and horses to allow studies to be performed on conscious animals.<sup>5,28-31</sup> Amphibian mucosa was the first tissue used in the "in vitro" studies that provided the cardinal information about the acid transporting ATPase.<sup>32</sup> Subsequent cellular studies have been performed on canine, equine, rabbit, and rat gastric glands.<sup>22,32-36</sup> Initially, food and food extracts were selected to stimulate gastric secretion, later histamine and alcohol were used in many studies.<sup>8,26,27</sup> Histamine continues to be a valuable

secretagogue for investigation of the acid secretory process and its regulation.<sup>1,20,29,30</sup> After Gregory and Tracy found that an extract of porcine antral mucosa was an effective stimulant of acid secretion<sup>9</sup>, gastrin became a popular investigational tool.<sup>28</sup> A synthetic polypeptide analog to the C terminal tetrapeptide of gastrin is pentagastrin, or peptavlon, which has become the secretagogue most commonly used for stimulation of gastrin related secretion.<sup>17-19,21,30,31</sup> Today, gastric secretory studies range from chronically implanted gastric cannulas in intact animal models to receptor immunochemical studies on ECL cells isolated from the gastric mucosa.

The hundreds of studies of gastric acid secretion have accumulated a vast amount of information with marked similarities in the process and its regulation. However, some striking differences have also been observed. The relative sensitivity to specific secretagogue, the rate of basal secretion, the response to inhibition, and ECL cell shape and prevalence are markedly different between species.<sup>17</sup> In the rat, the gastric acid secretory process is highly sensitive to pentagastrin and very resistant to histamine.<sup>17,30</sup> Histamine and gastrin are equally effective

on canine mucosa;<sup>17,30</sup> in rabbits histamine is much more effective than gastrin.<sup>17,30</sup> Basal secretion is minimal in dogs and cats and high in rats and rabbits, whereas humans, primates, pigs, and horses fall somewhere in between.<sup>17,28-31</sup> Maximal acid outputs on a normalized bodyweight basis induced by either histamine or pentagastrin, also differ between species. Maximal histamine-stimulated output is greater in rabbits than dogs, while in dogs it is greater than that of rats, pigs, and cats, which in turn, have rates of secretion markedly greater than that of primates and man.<sup>17,29,30</sup> During pentagastrin-induced acid secretion, rabbit and dog have a comparable maximal response, but that of rats is significantly less.<sup>30</sup> As with histamine, pig, rat, and cat maximal acid secretory rates in response to pentagastrin are comparable.<sup>29,30,37,38</sup> Maximal acid output is used to determine the necessary dosage of either secretagogue for the purpose of most experimental work; however, the gastric contents collected during these studies consist of fluid containing many electrolytes, pepsin, mucus and other substances, as well as acid.

The electrolyte composition of gastric secretion other than H<sup>+</sup> also changes with the secretory rate. The secretory

pattern has been examined with both histamine and pentagastrin in experimental models<sup>39-41</sup> and in patients with gastroduodenal diseases.<sup>42</sup> In man, the infusion of either histamine or pentagastrin results in similar changes in gastric electrolyte concentrations and outputs. Sodium concentration decreases and output remains constant, while potassium concentration increases slightly and output increases significantly. The concentration of calcium and phosphate decreases and outputs are unchanged.<sup>39</sup> Acid and sodium concentrations have a strong inverse correlation under these stimulatory conditions.<sup>39</sup> The histamine-stimulated maximal acid output in dogs is greater than that of pentagastrin; however, peak acid output is reached more quickly with pentagastrin than with histamine.<sup>41</sup> Sodium ion concentration is inverse to acid in the canine studies just as in human studies.

Thus, gastric secretions are a combination of parietal and nonparietal fluids. The parietal component is isotonic HCl that is secreted in response to specific secretagogues at a rate that increases significantly with stimulation of the parietal cell.<sup>4</sup> The nonparietal component is believed to be a constantly secreted isotonic ultrafiltrate of

plasma.<sup>43</sup> No change in nonparietal secretory rate is observed during stimulation with any of the known gastric secretagogues. Sodium ions are the predominate cation of this nonparietal component. The differences in response to secretagogues of these two components explains the inverse relationship of sodium and acid concentrations reported during increasing acid secretory rates.<sup>43</sup>

Various gastroduodenal diseases are characterized by alterations in the electrolyte composition of gastric contents.<sup>42</sup> Patients with active duodenal ulcers have increased acid and chloride concentration and decreased sodium concentration, while gastric ulcer patients have increased sodium concentrations in the gastric content without changes in the concentrations of acid, potassium, or chloride.<sup>42</sup> Other changes in the composition of electrolytes are suggestive of trophic gastric ulcers, chronic gastritis, and Zollinger-Ellison syndrome.<sup>42</sup> The characteristic gastric secretory response to stimulated gastric secretion has been consistently observed in all species except the horse.<sup>44</sup>

Due to the relative difficulty in collecting the contents, little was known about equine gastric secretion

until the 1980s. The apparent increase in gastric and duodenal ulcer disease in horses provoked a particular interest in equine gastric physiology.<sup>31,44</sup> Gastric mucosal ulceration has been observed in horses as a sequela to the administration of nonsteroidal anti-inflammatory drugs, and as a spontaneously occurring problem of unknown etiology.<sup>44-47</sup> Intermittent aspiration of gastric contents via nasogastric tube, placement of indwelling pH probes nasogastrically, and chronic indwelling gastric cannulas to collect contents by drainage have been used in recent studies of equine gastric secretion.<sup>31,44,48-52</sup> Only the cannula allows complete collection of gastric contents, but these studies can only be performed on fasted animals. Intermittent aspiration also requires fasted horses, but may not collect gastric contents in their entirety. The indwelling pH probe makes it possible to monitor the intragastric environment for a long periods of time in either fed or fasted states.

Basal secretion in horses has been described as continuously variable, with periods of spontaneous alkalinization as has also been observed in humans, pigs, rodents, monkeys, and chickens.<sup>31,44,48,50</sup> Thus, the hydrogen ion concentration and acid output range widely during

unstimulated gastric collection periods.<sup>31,44</sup> The basal equine acid output of approximately 30% of maximal output is consistent with pigs and rats, and it is greater than that of humans.<sup>44</sup> On a body weight basis, equine basal acid output over time is similar to that found in man.<sup>39,44</sup>

Up to now, pentagastrin has been the only secretagogue used "in vivo" to stimulate equine gastric acid secretion to characterize the species-specific responses and to study drugs designed to prevent or treat gastric ulcers.<sup>48,49,51,53,54</sup> Its administration to horses results in a significant increases in both gastric acid and sodium outputs.<sup>44</sup> Acid concentration increases after stimulation, but not to the maximal magnitude observed in other species. In addition, the increased sodium output during stimulation is unique to horses. As the dose of pentagastrin is increased, the concentration of sodium decreases slowly and remains greater than the acid concentration, unlike in other species where the sodium concentration rapidly decreases in an inversely proportional relationship to the increasing acid concentration.<sup>44</sup> This is a major species-specific difference in the equine secretory response to pentagastrin. Thus, it has been suggested pentagastrin stimulates both the

parietal and nonparietal components of gastric secretion in the horse.<sup>44</sup> A variety of compounds have been shown to inhibit equine basal and pentagastrin-stimulated gastric acid secretion, such as histamine H-2 antagonist ranitidine, the proton pump blocking agent omeprazole, and the prostaglandin misoprostol.<sup>31,48,49,51,53,54</sup> The profound sodium rich nonparietal secretion characteristic of the equine response to pentagastrin is evident even after omeprazole has effectively inhibited the acid secretory response.<sup>51</sup> The origin of this voluminous nonparietal component of gastric contents has not been clearly defined.

The periods of high pH of gastric contents during basal secretion have raised much speculation about the equine gastric secretory capacity, gastric emptying rates, and the buffering capacity of the various secretory products.<sup>50</sup> Potential buffering fluids include saliva, gastric nonparietal secretions, and duodenogastric reflux.<sup>44</sup> Saliva is not a likely candidate since the production of saliva in the horse is minimal except during mastication.<sup>55</sup> Fasting equine gastric contents are frequently dark green to yellow in color and viscous, suggesting possible contamination with bile.<sup>44</sup> Duodenogastric reflux has been observed during

endoscopic examination of the stomach.<sup>51</sup> The fluid refluxed could potentially contain a mixture of biliary, pancreatic and duodenal secretions, since the duodenal diverticulum, where the bile and minor pancreatic ducts enter, is in relatively close proximity to the pylorus.<sup>51</sup> Furthermore, the absence of a gallbladder leads to continuous secretion of bile in horses and equine pancreatic secretion is reported to be profuse and continuous.<sup>55,56</sup>

Pancreatic secretion of the horse is distinct from that of other species. The resting secretion of approximately 25  $\mu\text{l/g gland/min}$  is increased by four to fivefold during eating, stimulation of the vagus nerve, or after the administration of secretin or pentagastrin.<sup>55,57</sup> Neither resting nor vagal-induced pancreatic secretion is abolished by atropine.<sup>55,58</sup> Vagotomy does not alter the basal secretion. Studies with ponies fitted with re-entrant cannula in the pancreatic duct found that they may secrete a volume equivalent to up to 10% of their own body weight daily.<sup>55</sup> The concentration of amylase and the proteolytic activity of equine pancreatic juice is particularly low, and it has a very weak ability to emulsify fat, compared to other species.<sup>55</sup> Small increases in the concentration of

amylase are found during stimulation of the vagus, or during secretin or pentagastrin administration. The concentration of sodium and potassium are similar to respective plasma concentrations and chloride is the predominate anion at all levels of secretion. The bicarbonate concentration is low relative to other species and does not increase to the extent anticipated when the volume of secretion increases.<sup>55</sup> That is, in most species, the concentration of bicarbonate is less than chloride concentration at rest, but increases to become the predominate anion during maximally stimulated secretion.<sup>55</sup> The composition of the large non-parietal component of the fasting gastric contents is also similar to that of equine pancreatic fluid. Therefore, the observed species-specific particulars of equine pancreatic juice contents might explain the voluminous fluid response observed during pentagastrin-stimulated gastric collection.

The pancreas is a multifunctional organ which is responsible for the secretion of fluid, electrolytes, and enzymes essential to the normal digestive process and the endocrine secretion of hormones critical to metabolic homeostasis.<sup>59</sup> Just as with gastric secretion, pancreatic secretion has traditionally been divided into basal and

meal-induced patterns, with meal related secretion further divided into cephalic, gastric, and intestinal phases.<sup>60</sup> In most species, basal enzyme secretion ranges from 10% to 30% of maximal secretion, whereas, basal bicarbonate secretion is only 1% to 2% of maximal.<sup>60</sup> The regulation of basal enzyme secretion appears to vary between species, while basal bicarbonate secretion is dependent primarily on secretin augmented by cholinergic neural input.<sup>60</sup> Basal enzyme secretion is almost entirely due to cholinergic stimulation in the rat, whereas, in man, both CCK and cholinergic stimulation mediate it. Brief bursts of pancreatic enzyme and bicarbonate secretion are associated with the migrating myoelectric complex and a circadian rhythm has also been reported.<sup>60</sup> The normal pancreatic secretory response to a meal is increased enzymatic secretion to aid digestion and increased bicarbonate secretion to buffer the chyme and assure the optimum intraluminal pH for enzymatic activity. As with gastric secretion, "cephalic" pancreatic secretion seems to be stimulated either directly or indirectly by the vagus nerve.<sup>50</sup> "Gastro-pancreatic reflexes" are initiated by food or gastric distension and mediated by cholinergic vagovagal

reflex.<sup>50</sup> The two classical pancreatic regulatory hormones, cholecystokinin (CCK) and secretin, and vagal cholinergic reflexes are involved in the "intestinal" phase.<sup>60</sup>

Postganglionic cholinergic neurons are important in the regulation of enzyme and bicarbonate secretion by the release of acetylcholine at muscarinic receptors. Secretin is the most potent stimulant of the bicarbonate-rich fluid component of exocrine pancreatic secretion in dogs, cats, rats, and humans., while the primary hormonal stimulant of enzyme secretion is CCK.<sup>59,60</sup> In the rat, rabbit, pig and guinea pig, CCK is responsible for a copious fluid and electrolyte secretion which may have a low concentration of bicarbonate and a high concentration of chloride.<sup>59</sup> Enzyme secretion is stimulated by the action of CCK at CCK-A receptors on pancreatic acinar cells.<sup>61</sup> Although CCK-B/gastrin receptors have been identified on pancreatic acinar cells, their function remains unknown.<sup>61</sup> Caerulein is even more potent than CCK, and both are significantly more potent than gastrin, at stimulating pancreatic enzyme and fluid secretion in dogs.<sup>62</sup> A multitude of other receptors are present on pancreatic acinar cells, including those to bombesins, tachykinins, VIP, somatostatin, insulin,

endothelin, insulin-like growth factor and epidermal growth factor.<sup>61</sup> Much of the electrolyte secretion by the pancreas is secreted by duct cells rather than acinar cells.<sup>63</sup> The electrolyte composition of pancreatic secretions vary with the rate. Bicarbonate and chloride concentrations have a reciprocal relationship, but the cumulative anion concentration remains constant.<sup>63</sup> As the secretory rate increases, bicarbonate concentrations increase and chloride concentrations decrease.<sup>63</sup> The volume of the secretion in response to secretin vary with species. Cats, dogs, pigs and man have greater secretory rates per gram of gland than rats and rabbits.<sup>63</sup> The specific differences observed in the limited studies on equine pancreatic secretion are unique to the horse and similar secretory patterns have not been reported in other species.

#### Development of Hypothesis

After reviewing the overwhelming information about gastric secretory physiology in general, and equine gastric secretion specifically, it is apparent that equine gastric physiology requires still more investigation. The

development of a silastic indwelling gastric cannula by Campbell-Thompson and Merritt for the collection of equine gastric secretions was pivotal. The distinct composition of equine gastric contents, particularly the uncharacteristic "non-parietal" response to pentagastrin stimulation, is of special interest. Since pentagastrin has been the only exogenous secretagogue utilized to date in equine secretory studies, it would be of interest to see if the horse responded to other secretagogues in a similar way. Therefore, the initial project for this series of studies was to characterize the equine gastric secretory response to histamine. Pilot studies were performed with moderate trepidation due to the potential side effects of histamine administration to horses. These studies required pretreatment of the horses with a H-1 antagonist, pyrilamine maleate. The results of a small pilot study were the last key to the development of a hypothesis for this dissertation.

Histamine-stimulated equine gastric contents were markedly different than those following pentagastrin stimulation reported in previous studies. The mean acid and sodium concentrations from the pilot study are presented

in Table 1. It was apparent from these studies that the horse is capable of developing the "classical" parietal response to an acid secretagogue that is comparable to that of other monogastric species. During histamine stimulation, the maximal acid concentration values were much greater than those induced by pentagastrin, and sodium concentrations decreased in the classical reciprocal relationship to acid. The sodium output over various doses of histamine was constant, unlike the pentagastrin responses. Yet, the maximal acid output provoked by histamine was equivalent to that of pentagastrin stimulated secretion. These pilot findings made it evident that the stimulation of gastric acid secretion with histamine could be safely performed in horses, with certain precautions, and that well-designed dose response study was needed. This led to the study described in chapter 2. The predominant conclusion of early investigation of histamine stimulation was that, as opposed to pentagastrin, it induced a purely parietal gastric secretion in horses.

Table 1.  
Acid and Sodium Concentration during Histamine Infusion  
(n=4 horses)

| Histamine<br>Dose<br>$\mu\text{g/kg-hr}$ | Mean $[\text{H}^+]$<br>$\text{mEq/L}$ | Mean $[\text{Na}^+]$<br>$\text{mEq/L}$ |
|------------------------------------------|---------------------------------------|----------------------------------------|
| Basal                                    | 26.5                                  | 101.3                                  |
| 15                                       | 73.9                                  | 57.8                                   |
| 30                                       | 95.1                                  | 55.5                                   |
| 45                                       | 97.5                                  | 52.4                                   |

In order to perform controlled comparisons between histamine and pentagastrin, without potential extraneous factors, it was necessary to evaluate the secretory response to pentagastrin following pyrilamine maleate pretreatment. Chapter 3 presents the unexpected results of that study.

Four crucial facets of equine gastric secretion were considered to develop the dissertation hypothesis. First, equine basal and pentagastrin-stimulated gastric secretion has an uncharacteristically low concentration of acid and high concentration and output of sodium. Second, acid blockade with numerous agents does not eliminate the profound sodium-rich nonparietal component of pentagastrin-stimulated secretion. Third, Hickson and Alexander reported

that equine pancreatic water and electrolyte secretion is profuse and continuous and can be stimulated by pentagastrin. Finally, the stimulation of gastric secretion with histamine resulted in purely parietal secretion resembling that of other species. Therefore, the dissertation hypothesis is as follows. *In the equine gastric cannula model, the vigorous sodium-rich component of pentagastrin stimulated gastric contents is extragastric in origin.*

A technique of duodenal catheterization through the chronic gastric cannula was developed to allow for occlusion of the pylorus during acid secretory studies. Chapter 4 discusses the technique for duodenal catheterization, the effect of the technique on gastric secretion, and the composition of duodenal contents. The primary study of this dissertation, describing results with and without the obstruction of the pylorus, is presented in chapter 5 and was designed to definitively determine if the sodium rich fluid found during pentagastrin stimulation and absent during histamine stimulation is secreted by the gastric glandular mucosa or by a extragastric source.

## CHAPTER 2

### EQUINE HISTAMINE DOSE-RESPONSIVE GASTRIC ACID SECRETION

#### Introduction

Previous studies of equine gastric physiology have all utilized pentagastrin to stimulate gastric secretion.<sup>44,50,52</sup> Increased recognition of clinical disease in horses due to gastric and duodenal ulceration has led to interest in the potential use of horses as a model for peptic ulcer disease in humans as well as a desire to increase our knowledge about horses, themselves. Gastric ulceration has been shown to be a widespread phenomenon in horses and foals.<sup>64</sup> Compared to other species, pentagastrin-stimulated gastric contents in horses differs by being relatively low in acid concentration and high in sodium concentration, even at maximal secretory responses.<sup>44</sup> Nevertheless, the inhibition of pentagastrin-stimulated gastric acid secretion has been an important and effective means to evaluate therapeutic potential of various anti-ulcer agents in this species.<sup>31,49</sup>

Histamine-2 receptor antagonists have been used successfully to treat horses with clinical signs related to gastric ulceration.<sup>64</sup>

In order to better characterize equine gastric physiology, investigation of the effects of a secretagogue other than pentagastrin is essential. Histamine seems the obvious choice, but its use in horses has been avoided due to the presumed equine respiratory and CNS hypersensitivity to this agent. Ideally, "Histalog", a specific H-2 agonist, might be used, but it is no longer available. In other species, the undesirable side-effects of histamine have been largely avoided by pretreatment with an H-1 antagonist<sup>29</sup>, and such a protocol was chosen for the studies described herein. Specific objectives of the study were to: 1) determine the dose of histamine needed to elicit a maximal acid secretory response in the horse and how equidae compare with other species, and; 2) see if the non-parietal component of the secretory response to histamine is similar to, or different from, that seen with pentagastrin stimulation.

### Materials and Methods

Six adult horses, both mares and geldings, were used. All studies were done with the approval of the University of Florida IACUC. The horses ranged from 2 to 20 years of age. The five Thoroughbreds, and one Arabian weighed an average of 484 kg (range 444-506 kg). All horses were free of clinical signs of gastrointestinal disease, were dewormed every 2 months and were vaccinated for encephalitis and tetanus every 6 months. They were maintained on grass pasture with coastal hay ad lib and 12% protein grain twice daily. Each horse was previously prepared with a chronic indwelling gastric cannula as described by Campbell-Thompson and Merritt.<sup>31</sup>

The horses were fasted with free choice water for 20 hours prior to each experiment. At least one week interval occurred between experiments on any given horse. Studies were performed while the horse was loosely restrained in the laboratory.

After placement of an indwelling jugular catheter, the gastric cannula was opened and drained by gravity for 30

minutes allowing emptying of residual gastric contents. During the experiments, gastric contents were collected in 15 minute aliquots. The volume was measured to the nearest 5 ml in a graduated cylinder. Samples were filtered through gauze to remove feed particles and foam. The pH was determined using a glass electrode (Radiometer, Copenhagen, Denmark) calibrated at 20°C using commercial buffer solutions of pH 2 and 7 (pH standard, Fisher Scientific). Hydrogen ion concentration was measured in duplicate by electrometric titration with 0.1N NaOH to an endpoint of 7.4. (Radiometer, Copenhagen, Denmark) Sodium ion concentration was measured by flame photometry (Instrumentation Laboratories Inc., Lexington, MA) on samples diluted in an internal standard lithium solution (Dilumat, Fisher Scientific). The machine was calibrated with known  $[Na^+]/[K^+]$  standards (Instrumentation Laboratories Inc., Lexington, MA) prior to analysis and after every 5 samples. Acid and sodium outputs were calculated for each time period on a per kg body weight basis.

The first three 15-minute time periods were during basal (no treatment) gastric collections. At time  $t=45$

minutes, pyrilamine maleate ("Histavet-P", Schering-Plough, NJ) was infused IV at 1 mg/kg over the entire 15 minute collection period. No treatment was given during the subsequent two collection periods (t=60-90 minutes). Histamine infusion (7.5  $\mu$ g/kg-hr) was begun at time t=90 minutes and continued for 60 minutes. Two additional 60 minute infusions of histamine, of 15  $\mu$ g/kg-hr and 30  $\mu$ g/kg-hr respectively, followed. Therefore, the whole experiment lasted for 4.5 hours.

Crystalline histamine (Sigma Chemical Co., St. Louis Mo) was dissolved in 60 mls of 0.9% NaCl and filtered through a 0.22  $\mu$ m cellulose nitrate filter (Corning, Corning NY) in preparation for infusion, given by infusion pump. (Harvard Apparatus, South Natick MA)

In a separate trial, the horses were maximally stimulated with pentagastrin<sup>44</sup> for collection of data for comparison. The horses were prepared as described for histamine trial. After two hours of basal collection, pentagastrin was infused at 6  $\mu$ g/kg-hr for two hours. Gastric collections were analyzed as during the histamine trials.

Maximal acid output per histamine dose was calculated from the last two 15-minute collections at each dose. Values were expressed as  $\mu\text{Eq/kg BW/15 min}$ . Results are presented as mean and SEM for all parameters. Data were subjected to one-way analysis of variance for repeated measures. A significance value of  $p \leq 0.05$  was selected. Pairwise multiple comparison testing of significance was performed using Student-Newman-Keuls test. Acid output vs. sodium output data were subjected to linear regression for comparison to respective pentagastrin-stimulated outputs from the same horses.

### Results

The horses used had been involved in gastric secretory studies for at least one year prior to these studies. They demonstrated no evidence of gastrointestinal disease or problems related to the gastric cannula. Endoscopic examination of the gastric and duodenal mucosa as a part of another project in the laboratory revealed an occasional *Gastrophilus* spp. larvae and healthy intact gastric squamous and glandular mucosas.

Two horses did not complete the entire experiment. In one experiment, the infusion had to be terminated after the 15  $\mu\text{g/kg-hr}$  histamine infusion period because the horse developed marked muscle tremors and mild abdominal contractions. After the infusion was stopped, the gastric cannula closed and hand-feeding begun, the horse recovered rapidly. Thirty minutes into the 30  $\mu\text{g/kg-hr}$  infusion into a second horse, it developed generalized muscle tremors and mild synchronous diaphragmatic flutter. It became clinically normal within 20 minutes of ending the experiment and being allowed to eat.

#### Basal Secretion

Contents collected under pretreatment (basal) conditions were generally yellow-tinged, viscid, and cloudy. The 15-minute aliquots ranged in volume from 280 to 640 mls, with a mean of  $428.3 \pm 34.1$  mls/15 min. The mean acid concentration was  $42.5 \pm 3.9$  mEq/L, and mean acid output was  $39.8 \pm 6.6$   $\mu\text{Eq/kg BW/15 min}$  with a range from 19.3 to 82.7  $\mu\text{Eq/kg/15 min}$ . The pH of the samples varied greatly between 1.38 and 2.01, with a mean of  $1.67 \pm 0.036$ . The mean sodium concentration was  $75.7 \pm 7.2$  mEq/L, and mean sodium

output was  $68.2 \pm 8.2$   $\mu\text{Eq/kg BW/15 min}$  with a range from 17.7 to 101.7  $\mu\text{Eq/kg/15 min}$ .

TABLE 2.

Data from Equine Gastric Contents Collected Before and After Histamine Infusion.

|                                              | BASAL            | POST-PYRILAMINE  | 7.5 ( $\mu\text{g/kg-hr}$ ) | 15 ( $\mu\text{g/kg-hr}$ ) | 30 ( $\mu\text{g/kg-hr}$ ) |
|----------------------------------------------|------------------|------------------|-----------------------------|----------------------------|----------------------------|
| Volume (mls/15 min)                          | $428.3 \pm 34.1$ | $356.7 \pm 37.3$ | $591.7 \pm 41.4$<br>a,b     | $591.7 \pm 28$<br>a,b      | $508.9 \pm 54.8$<br>a,b    |
| pH                                           | $1.67 \pm 0.036$ | $1.79 \pm 0.08$  | $1.46 \pm 0.09$             | $1.48 \pm 0.13$            | $1.29 \pm 0.03$            |
| Peak $[\text{H}^+]$ (mEq/l)                  | $42.5 \pm 3.9$   | $33.5 \pm 3.5$   | $72.2 \pm 3.9$<br>a,b       | $81.3 \pm 5.1$<br>a,b,c    | $82.9 \pm 6.8$<br>a,b,c    |
| Peak Acid Output ( $\mu\text{Eq/kg/15min}$ ) | $39.8 \pm 6.6$   | $25.9 \pm 4.4$   | $87.9 \pm 7.7$<br>a,b       | $99.5 \pm 8.1$<br>a,b,c    | $98.4 \pm 4.2$<br>a,b,c    |
| Peak $[\text{Na}^+]$ (mEq/l)                 | $75.7 \pm 7.2$   | $79.5 \pm 7.5$   | $48.8 \pm 5.8$<br>a,b       | $46.7 \pm 6.2$<br>a,b      | $39.1 \pm 9.0$<br>a,b      |
| Peak Na Output ( $\mu\text{Eq/kg/15min}$ )   | $68.2 \pm 8.2$   | $60.6 \pm 9.6$   | $61.7 \pm 8.8$              | $58.5 \pm 9.4$             | $50.3 \pm 14.7$            |

Values expressed as Mean  $\pm$  SEM

Pairwise Multiple Comparison procedure-Student-Newman-Keuls

a-significantly different ( $p < 0.05$ ) than basal

b-significantly different ( $p < 0.05$ ) than post-pyridylamine

c-significantly different ( $p < 0.05$ ) than 7.5  $\mu\text{g/kg-hr}$

Peak values derived from the final 30 minutes of each treatment.

### Pyrilamine Infusion

The volume of contents collected ranged from 70 to 550 mls, with a mean of  $356.7 \pm 37.3$  mls/15 min and was not significantly different than basal collections. The mean acid concentration was  $33.5 \pm 3.5$  mEq/L, mean sodium concentration was  $79.5 \pm 7.5$  mEq/L, and mean sodium output was  $60.6 \pm 9.6$   $\mu$ Eq/kg BW/15 min. Acid output ranged from 3 to 55  $\mu$ Eq/kg BW/15 min, with a mean of  $25.9 \pm 4.4$   $\mu$ Eq/kg BW/15 min. These results were not significantly different from the basal time periods.

### Histamine dose-response

Gastric collections became progressively more clear as acid concentration increased. During maximal histamine stimulation, the contents were colorless and watery.

### Volume

Maximal secretory volumes ranged from 360 to 850 ml/15min. For each increasing dose of histamine, the mean volume was 591.7, 591.7, and 508.9 ml/15min, respectively. The volume collected during each dose of histamine infusion was significantly greater ( $p < 0.0001$ ) than basal volume;

however, the stimulated volumes did not differ significantly among doses.

#### Acid Concentration

The mean acid concentration during basal and increasing histamine infusion doses showed the expected vigorous response to the treatments. Maximal acid concentration (MAC) ranged from 51 to 110 mEq/L, and mean MAC was significantly greater ( $p < 0.0001$ ) than basal acid concentration at all doses. Acid concentration at all doses was also significantly greater ( $p < 0.05$ ) than during the post-pyrimidine period. The  $[H^+]$  during the 7.5  $\mu\text{g/kg-hr}$  infusion was significantly lower ( $p < 0.05$ ) than during either the 15 or 30  $\mu\text{g/kg-hr}$  infusion. The MAC during 15 and 30  $\mu\text{g/kg-hr}$  infusions did not differ significantly.

#### Acid Output

Acid output (AO) for each treatment was calculated as the mean of the final two 15 minute collections of each infusion period. The individual highest AO was 155  $\mu\text{Eq/kg BW/15 min}$  occurring at  $t=195$  min during the 15  $\mu\text{g/kg-hr}$  histamine infusion. The AO in response to all histamine doses was significantly greater ( $p < 0.0001$ ) than basal

output, and was the greatest during the 15  $\mu\text{g/kg-hr}$  infusion. However, there was no significant difference between the responses to 15  $\mu\text{g/kg-hr}$  and 30  $\mu\text{g/kg-hr}$  infusions, whereas both the 15 and 30  $\mu\text{g/kg-hr}$  infusion resulted in an AO significantly greater ( $p < 0.05$ ) than that from the 7.5  $\mu\text{g/kg-hr}$  infusion.

#### Sodium concentration

The sodium concentration was inversely related to acid concentration and ranged from 48.8 mEq/L to 39.1 mEq/L. The mean sodium concentration was significantly less ( $p = 0.000119$ ) during the 15 and 30  $\mu\text{g/kg-hr}$  histamine infusion than during the basal period. The 7.5  $\mu\text{g/kg-hr}$  infusion resulted in  $[\text{Na}^+]$  significantly greater than either the 15 or 30  $\mu\text{g/kg-hr}$  infusion and not significantly different from either basal or post-pyrimidine periods. The concentration of  $\text{Na}^+$  in collections during the 15 and 30  $\mu\text{g/kg-hr}$  infusions did not differ significantly from one another.

### Sodium Output

Mean maximal sodium outputs decreased from  $61.7 \pm 8.8 \mu\text{Eq/kg/15 min}$  to  $50.3 \pm 14.7 \mu\text{Eq/kg/15 min}$  as the histamine infusion rates increased from  $7.5 \mu\text{g/kg-hr}$  to  $30 \mu\text{g/kg-hr}$ . No significant differences were observed in the sodium output during basal, post-pyridamine or histamine-stimulated collection periods.

### Pentagastrin Outputs

The mean maximal acid output during pentagastrin infusion was  $91.8 \pm 3.5 \mu\text{Eq/kg/15 min}$ . Corresponding mean peak sodium output during the pentagastrin trial was  $100.8 \pm 5.0 \mu\text{Eq/kg/15 min}$ .

### Discussion

As in other species, intravenous administration of histamine base stimulated gastric acid secretion in horses resulting in maximal acid outputs (MAO) comparable to those of pentagastrin-stimulated horses. Infusions were performed without serious complications. Pretreatment with pyridamine

maleate, a selective H-1 receptor blocking agent<sup>11</sup>, presumably eliminated any potential respiratory or neurologic side-effects of histamine infusion.

Histamine-induced dyspnea results from bronchoconstriction mediated by H-1 receptors.<sup>11</sup> Both H-1 and H-2 receptors are located in the central nervous system and horses are more susceptible to pronounced excitation and anxiety than some other species. The histamine provocation test for studies of equine bronchial responsiveness requires sedation to prevent apprehension and anxiety.<sup>65</sup>

Two experiments were not completed because the horses developed synchronous diaphragmatic flutter (SDF) and muscle twitches. It is our belief that this was due to metabolic alkalosis with hypocalcemia and hypochloremia following marked HCl secretion.<sup>66</sup> Changes in the ionization potential during metabolic alkalosis alter the free to bound calcium ratio and results in SDF.<sup>66</sup> Once stimulation of HCl secretion ceased and the cannula was occluded, fluid and electrolyte loss ended and the horses responded rapidly. These individual horses were apparently hyper-responsive to histamine, since the MAO was reached during the 7.5  $\mu\text{g/kg-hr}$  infusion in one horse and after the first 15

minutes of the 15  $\mu\text{g/kg-hr}$  infusion in the other. These horses did not exhibit long-term effects following these episodes, and subsequent histamine infusions were administered to them without incident.

Antihistaminic agents, such as pyrilamine maleate, specific to H-1 receptors are not expected to have antisecretory effects and are routinely used as part of the histamine challenge of gastric secretion in humans.<sup>11</sup> A post-pyrilamine decrease in acid concentration and output was consistently observed and could reflect receptor cross-reaction or changes in blood flow to the gastric mucosa, since both H-1 and H-2 receptors are involved in histamine effects on vasculature.<sup>11</sup> H-1 receptor blockade may also affect the delivery of substances to the basolateral membrane of parietal cells, since H-1 receptors are involved in the regulation of capillary permeability.<sup>11</sup>

The results indicate that a histamine dose of 30  $\mu\text{g/kg-hr}$  can be considered as that which will induce a maximal gastric acid secretory response in the horse. (See fig.1) In pilot studies for this trial, horses were infused with 15, 30, and 45  $\mu\text{g/kg-hr}$  of histamine. However, some of these horses exhibited signs of metabolic alkalosis

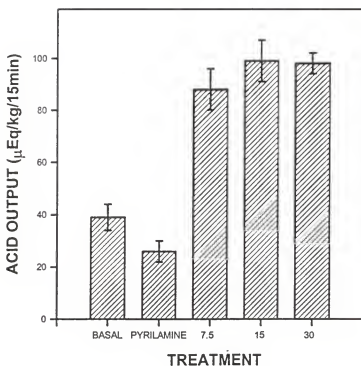


Figure 1. Mean acid output/15 min. during the last 30 minutes of each treatment. "Basal" indicates the status prior to any treatment. "Pyrilamine" indicates the output after treatment with pyrilamine maleate (1 mg/kg IV) and peak outputs during IV histamine infusion of 7.5, 15, and 30  $\mu$ g/kg-hr are indicated accordingly. Data are expressed as mean  $\pm$  SEM.

during the 45  $\mu$ g/kg-hr infusion; therefore, we elected not to utilize this higher dose in this trial. Four horses completed the pilot study and the MAO during the 45  $\mu$ g/kg-hr infusion was not significantly different from the MAO during

30  $\mu\text{g/kg-hr}$  infusion in these horses. (unpublished results) As with other species<sup>29,41</sup>, some individual horses were maximally stimulated at lower doses, but there was no "supramaximal depression"<sup>40,67</sup> of the mean response seen when the dose was increased from 15 to 30  $\mu\text{g/kg-hr}$ . Thus, the horse is apparently slightly more sensitive to histamine than man, in which the infusion of 42  $\mu\text{g/kg-hr}$  results in MAO(1); the pig and dog are more resistant, requiring 60  $\mu\text{g/kg-hr}$ <sup>29</sup> and 50  $\mu\text{g/kg-hr}$ <sup>24</sup>, respectively. The peak secretory response to histamine in horses was more gradually attained than the response to pentagastrin infusion.<sup>44</sup> This phenomenon has been previously reported in other species, as well.<sup>41</sup>

Mean maximal acid output in horses induced by histamine was similar to that seen in humans on mEq/kg basis. Furthermore, the maximal responses to histamine and pentagastrin are not significantly different in horses, as was anticipated. Species differences in maximal acid output and relative sensitivity to histamine and pentagastrin are numerous.<sup>17,68</sup> The majority of "in vivo" gastric secretory studies have involved dogs, rats, and humans.<sup>69</sup> Dogs have

minimal basal acid secretion, whereas humans and rats have active, though erratic, basal secretion, as do horses.<sup>44</sup>

The maximal acid secretory response to histamine and pentagastrin is equivalent in dogs and humans, while rats are much more sensitive to pentagastrin than histamine.<sup>17</sup>

It appears that horses may be very comparable to humans "in vivo," since they are equally responsive to both secretagogues and have similar basal acid secretory activity. (Table 3) "In vitro" studies of isolated parietal cells have demonstrated species differences in sensitivity to specific secretagogues. Canine parietal cells can be stimulated by carbachol, gastrin, or histamine, with carbachol being the most potent. Conversely, human and rat parietal cells are strongly stimulated by histamine and only weakly stimulated by gastrin and carbachol. The horse appears to be more like the human and rat, since histamine is the most effective secretagogue of isolated equine parietal cells, followed by gastrin and carbachol.<sup>34</sup>

TABLE 3.  
Acid and Sodium Concentrations  
Histamine versus Pentagastrin

| PARAMETER                | EQUINE<br>Pentagastrin<br>(PG) * |               | HUMAN<br>PG or HI** |               | EQUINE<br>Histamine<br>(HI) |               |
|--------------------------|----------------------------------|---------------|---------------------|---------------|-----------------------------|---------------|
|                          | Basal                            | Max.<br>Stim. | Basal               | Max.<br>Stim. | Basal                       | Max.<br>Stim. |
| [H <sup>+</sup> ] mEq/L  | 21-45                            | 35-57         | 10-40               | 70-120        | 28-45                       | 75-120        |
| [Na <sup>+</sup> ] mEq/L | 45-92                            | 75-146        | 30-70               | 15-30         | 62-123                      | 23-70         |

\* from ref no.66

\*\* from ref no.42

In this study, mean acid concentration during maximal histamine stimulation was markedly greater than that observed during maximal pentagastrin stimulation. Maximal acid concentrations in other species have ranged from 100-140 mEq/L<sup>17,39</sup>, irrespective of stimulant. Individual maximal acid concentrations in these horses ranged from 75-125 mEq/L during histamine infusion. In contrast, in pentagastrin stimulated horses, the maximal acid concentration rarely reached 75 mEq/L, which was reported<sup>44</sup> to be a major difference between horses and other species. Apparently, a nonparietal sodium rich fluid component of gastric secretion was strongly stimulated by pentagastrin.

Sodium outputs increased coincident with acid outputs during pentagastrin stimulation in horses<sup>44</sup>; whereas, in the studies described here, sodium concentration decreased as acid concentrations increased during histamine stimulation, and the sodium output was constant as the acid output increased to a maximal level. (fig.2) Thus, in the horse as in other species, histamine appears to stimulate a purely parietal secretion, with acid concentrations rising to expected levels and a reciprocal decrease in sodium concentration.<sup>39, 41</sup>

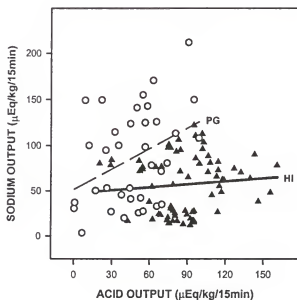


Figure 2. Regression analysis of acid vs. sodium outputs during pentagastrin (o) and histamine ( $\blacktriangle$ ) infusion.

The exact origin of the histamine which stimulates parietal cells and the mechanisms involved in its release have not been clearly documented in most species<sup>24</sup>, but it is known to act via H-2 receptors on parietal cells as a paracrine mediator.<sup>2,20</sup> In rats, enterochromaffinlike (ECL) cells are the major histamine source in the gastric mucosa and gastrin has been shown to stimulate its release from them.<sup>22,24</sup> Rabbit and human gastric mucosal preparations also release histamine in response to gastrin but the cells responsible have not been identified.<sup>22</sup> Few ECL cells are found in the normal human and canine mucosa; however, many mast cells are observed and may serve as the histamine source.<sup>24</sup> Human patients with hypergastrinemia appear to have increased numbers of ECL cells in their gastric mucosa.<sup>24</sup> The density of ECL cells in equine gastric mucosa is greatest in the pyloric gland region.<sup>70</sup> Fewer ECL cells have been identified in the fundic gland mucosa and in the proximal duodenum.

In this study, we determined that histamine can be used as a stimulant of gastric acid secretion in horses. Histamine stimulated mean maximal acid output was comparable to that previously reported with pentagastrin.<sup>44</sup>

In contrast, the mean maximal acid concentration in response to histamine was much greater than that observed during maximal pentagastrin stimulation. These findings suggest that in horses, histamine stimulates purely parietal secretion, while pentagastrin stimulates the production of gastric contents that appear to be both parietal and nonparietal in origin.

CHAPTER 3  
THE EFFECT OF PYRILAMINE MALEATE PRETREATMENT ON  
PENTAGASTRIN-STIMULATED EQUINE GASTRIC SECRETION

Introduction

The interaction between gastrin and histamine receptors has long been controversial.<sup>1,2,3</sup> The ability of histamine receptor antagonists to eliminate pentagastrin-stimulated gastric acid secretion supports the indirect action of gastrin on parietal cells.<sup>21,31,37,48,49,51,53,54</sup> This inhibition of gastric secretion has been limited specifically to histamine H-2 receptor antagonists. The administration of antihistamines directed at H-1 receptors has not been shown to suppress acid production during stimulation with various secretagogues, including pentagastrin.<sup>11,29,71</sup> Although differences in the relative sensitivity to various secretagogues have been observed between species, the characteristics of gastric contents during maximal stimulation with histamine or pentagastrin are similar, with the exception of the horse.

Equine gastric contents during maximal stimulation with histamine have a high concentration of acid and low concentration of sodium as is characteristic of parietal secretion in other species, (see Chap. 2) whereas, pentagastrin-stimulated equine gastric contents have a high concentration of sodium and a relatively low acidity.<sup>44</sup> Histamine stimulation of gastric secretion induces a maximal acid outputs (MAO) equal to those of pentagastrin-stimulated horses. (See Chap. 2) In horses, as in other species, it is necessary to administer an H-1 antagonist prior to histamine infusion to prevent side-effects.<sup>11,29,65</sup> During gastric secretory studies on horses stimulated with histamine, pretreatment with the H-1 antagonist, pyrilamine maleate, resulted in a short-lived decrease in basal volume, acid concentration and acid output. (See Chap.2) The effect of this pretreatment on pentagastrin-stimulated gastric secretion is thus far unknown. Since we planned to further investigate the species specific disparity in the histamine and pentagastrin-stimulated secretory responses, we designed this study to consider the effect of pyrilamine maleate pretreatment on pentagastrin-stimulated gastric secretion.

## Materials and Methods

### Horses

Two mixed breed, one Thoroughbred and one Arabian [2 mares, 2 geldings] ranging from 3 to 20 years were used in this study. The horses were all healthy and ranged in weight from 370 to 490 kg. They were maintained on grass pasture and provided coastal hay ad lib and 12% protein grain twice daily. All horses were dewormed every 2 months, vaccinated for encephalomyelitis and tetanus every 6 months and were free of clinical signs of gastrointestinal disease. Chronic indwelling gastric cannulas as described by Campbell-Thompson and Merritt<sup>31</sup> had been prepared in these horses 1 to 24 months prior to this study. All studies were approved by the University of Florida IACUC.

### Experimental preparation

Horses were fasted with free choice water for 20 hours prior to an experiment. Experiments were performed with no less than a one week interval between them. The horses were loosely restrained in the laboratory for the entire

experiment. The gastric cannula was opened and allowed to drain by gravity for 15 to 20 minutes, while a indwelling jugular catheter was emplaced. The gastric contents were collected into 1L fluid bags suspended from a surcingle.

#### Experimental protocol

Gastric contents were collected in 15 minute aliquots and were filtered through gauze prior to analysis. Collections were measured for volume and if available, a 50 ml sample was saved for further analyses. Analyses were performed either immediately or samples were frozen for later analysis. Each experiment lasted 3 hours. During the first 45 minutes [basal collection], no treatment was given. In the treatment experiments, pyrilamine maleate (Histavet-P, Schering-Plough NJ) was infused IV at 1 mg/kg over a 15 minute period, beginning at time  $t=45\text{min}$ . No additional treatments were given for 30 minutes. In the no treatment experiments, basal collection was continued during time  $t=45-90\text{ min}$ . At time  $t=90\text{min}$ , an IV infusion of pentagastrin [ $6\text{ }\mu\text{g/kg-hr}$ ] was administered by infusion pump

(Harvard Apparatus, South Natick MA) in all experiments and continued for the remainder of the experiment.

Each infusion was given in a volume of 60 ml/hr. Horses were weighed the morning of the experiment to determine the amount of pentagastrin needed. Pentagastrin was prepared by dissolving with 0.8 ml of DMSO and 90 mls of 0.9% NaCl and filtered through a 0.22  $\mu$ m cellulose nitrate filter (Corning, Corning NY) in preparation for infusion.

#### Sample analysis

Volume was measured in a graduated cylinder. Aliquots of gastric contents were analyzed immediately for hydrogen ion concentration, using a automatic titrator (Radiometer, Copenhagen Denmark). Hydrogen ion concentration of each aliquot was measured in duplicate by titration with 0.1N NaOH to an endpoint of pH of 7.4. Output was calculated on a per kg body weight basis from the volume and hydrogen ion concentration and was expressed as  $\mu$ Eq/kg/15 min.

### Analysis of data

Statistical analysis was performed on volume, acid concentration, and acid output data. The last 30 minutes of basal ( $t=30\&45$  min), post-pyrlamine ( $t=75\&90$  min), and two infusion-related collections (early:  $t=105,120\&135$  min; late:  $t=150,165\&180$  min) were compared between the studies with and without pyrlamine pretreatment. Since the same horses were used in each study, a paired  $t$ -test was performed for each of the four time periods. The time periods were not compared to each other. A  $p \leq 0.05$  was considered significant.

### Results

In both studies, the volume and acid output rapidly increased after pentagastrin infusion began. The horses had no adverse reactions during or following the administration of pyrlamine maleate. Physical characteristics of the gastric collections from both studies were the same. The mean and SEMs for each time period of both studies are shown in Table 4.

### Basal Collections

The volume, acid concentration, and acid output during the basal time period of both studies did not differ significantly.

### Post-Pyrimilamine Collections

In the pyrimilamine study, the volume collected during the 30 minutes following the administration of pyrimilamine was significantly less ( $p=0.0145$ ) than when no pyrimilamine was given. The acid concentration did not differ between studies. The acid output was significantly less ( $p=0.0008$ ) in the pyrimilamine study than when no pyrimilamine was given.

### Early Infusion Collections

The volume and acid concentration did not differ significantly between the studies, however, the acid output was significantly less ( $p=0.0274$ ) in the pyrimilamine studies than when no pyrimilamine was given.

TABLE 4.

Mean and SEM Data from Gastric Contents Collected Before and After Pentagastrin Infusion with and without Pretreatment with Pyrilamine Maleate.

|                                | PYRIL-AMINE | BASAL         | POST-PYRIL-AMINE | EARLY INFUSION * | LATE INFUSION ** |
|--------------------------------|-------------|---------------|------------------|------------------|------------------|
| VOLUME<br>(ml)                 | NO          | 253.8 ± 37.2  | 381.7 ± 29.9     | 585.8 ± 74.9     | 622.5 ± 43.7     |
|                                | YES         | 287.5 ± 27.95 | 181.7 ± 34.8 ★   | 415 ± 102.2      | 589.2 ± 71.0     |
| [H+]<br>(mEq/L)                | NO          | 31.14 ± 9.54  | 39.7 ± 11.0      | 31.2 ± 5.5       | 48.0 ± 5.6       |
|                                | YES         | 39.5 ± 6.1    | 31.7 ± 7.0       | 36.4 ± 9.0       | 51.6 ± 8.2       |
| ACID OUTPUT<br>(μEq/kg-15 min) | NO          | 18.1 ± 5.2    | 34.1 ± 7.5       | 46.4 ± 5.8       | 76.8 ± 5.6       |
|                                | YES         | 24.5 ± 3.9    | 12.4 ± 2.5 ★     | 26.7 ± 6.0 ★     | 56.5 ± 4.0 ★     |

\* First half of Pentagastrin Infusion (t=105,120,&135 min)

\*\* Last half of Pentagastrin Infusion (t=150,165,&180 min)

★ Significantly Less than during No Pyrilamine Study

#### Late Infusion Collections

As during early infusions, the volume and acid concentration were not significantly different between the two studies. Acid output was significantly greater (p=0.0031) in the study with no pyrilamine pretreatment.

## Discussion

Pentagastrin infusion resulted in secretion of gastric acid in both studies; however, the maximal acid output was affected by the administration of pyrilamine maleate. This finding was unexpected since pyrilamine pretreatment has been used as the pretreatment of choice when performing histamine stimulation in other species;<sup>11</sup> where the use of an H-1 specific receptor antagonist does not affect the secretion of gastric acid during stimulation. In part, the confusion over whether or not histamine acts directly on gastric mucosa resulted from early classical studies in which antihistamines were found to have no inhibitory effect on histamine induced gastric secretion.<sup>27</sup> Better understanding of histamine receptor classes has helped to clarify the role of histamine in gastric secretion and explain these earlier findings,<sup>11,12</sup> namely that parietal cells have H-2 receptors and histamine stimulated gastric acid secretion appears to be a H-2 specific response.<sup>1,2,3,68,69</sup>

Histamine receptors are involved in other aspects of gastric function as well as acid secretion. Three specific receptor types, H-1, H-2, and H-3 have, to date, been

recognized. As well as regulation of acid secretion, these receptors also play a role in the regulation of gastric microcirculation and motility.<sup>71</sup> Mucosal circulation is affected by histamine primarily via H-1 receptors, although H-2 and H-3 receptors may be involved. In the rat, for instance, it appears that both H-1 and H-2 receptors are involved in histamine related vasodilation.<sup>72</sup>

Vasoconstriction occurs with H-1 receptor stimulation in the rabbit.<sup>72,73</sup> Pyrilamine has been shown to competitively inhibit histamine related vasodilation in the guinea pig.<sup>73</sup> The changes, if any, in equine gastric circulation in response to histamine or histamine blocking agents are not known.

The importance of gastric mucosal circulation in the horse may be most clearly demonstrated by the relative sensitivity of the horse to gastric ulceration due to NSAID's, though no specific studies have quantified equine gastric mucosal blood flow or the regulation of flow. The administration of NSAID's results in gastric ulceration by inhibition of prostaglandins involved in mucosal blood flow and cytoprotection.<sup>47</sup> Gastrointestinal injury can be seen endoscopically in horses with or without accompanying

clinical signs within a few days of initiation of administration of even the recommended dose of phenylbutazone or flunixin meglumine.<sup>47</sup> Gastric microcirculation is a key component of gastric mucosal protection<sup>72</sup> and can be rate-limiting for gastric secretion.<sup>74</sup>

Secretagogues involved in stimulating gastric acid secretion result in increases in blood flow as well. Histamine, gastrin, and cholinergic agents produce vasodilator activity associated with the increasing secretory rate.<sup>75</sup> Blood flow has been shown to be rate-limiting at high levels of stimulation and agents which decrease blood flow will also inhibit acid secretion.<sup>75</sup> A histamine H-2 antagonist, such cimetidine, has been shown to decrease blood flow and acid secretion during pentagastrin stimulation in cats, however, mucosal blood flow was not decreased under basal conditions.<sup>37,72</sup> Although secretion is increased by pentagastrin stimulation in this study, the secretory response may be restricted by limitations on blood flow.

Histamine H-1 receptor antagonists may affect gastric microcirculation by action at histamine receptors or by

atropine-like activity at muscarinic receptors<sup>11,76</sup> involved in vasodilation. In dogs, the cholinolytic properties of pipolphen, a H-1 blocker, have been shown to suppress gastric secretions.<sup>77</sup> Agonist to H-3 receptors<sup>78-80</sup> and antagonist of the H-2 receptor<sup>11,12,31,78</sup> result in decreased acid secretion. Pyrilamine has been utilized in numerous secretion studies and in most species does not elicit this antiseecretory response.<sup>81,82,83</sup> In other equine studies, pyrilamine maleate administration was followed by a decrease in basal secretion, but this decrease was not always significant. (See Chap. 4 & 5)

Histamine H-3 receptors are found in several locations including the brain, perivascular nerve terminals, pulmonary airways, and ECL cells in the gastric mucosa.<sup>36,84</sup> These receptors appear to be involved in the autoregulation of histamine release from ECL cells during the stimulation of gastric acid secretion.<sup>1,24,36,79,80</sup> They may also be involved in the release of somatostatin which inhibits gastric acid secretion.<sup>78</sup> Certain drugs have demonstrated simultaneous H-1 agonist/H-3 antagonist properties,<sup>85</sup> however, it appears that pyrilamine has a low affinity for H-2 and H-3

receptors.<sup>86</sup> The distribution of H-1, H-2, and H-3 receptors in the horse has not been documented.

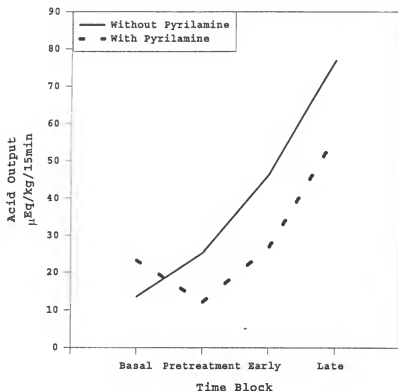


Figure 3 Mean pentagastrin stimulated acid output with and without pyrilamine pretreatment. "Basal" refers to acid output prior to any treatment. (t=30&45 min) "Pretreatment" indicates output after pretreatment with pyrilamine or from comparable period with no treatment. (t=75&90 min) "Early" represents the first half of pentagastrin infusion. (t=105,120&135 min) Output during the last half of pentagastrin infusion is labeled "late". (t=150,165&180 min)

In this study, maximal pentagastrin-stimulated acid output was significantly decreased in horses that received

pyrilamine prior to stimulation. This finding is contrary to the results in other species where H-1 receptor antagonist do not inhibit gastric acid secretion. Because the precise mechanism for this action is not clear, it is apparent that this may be yet another important equine specific finding that warrants further investigation.

Therefore, equine gastric secretion in response to pentagastrin differs not only in composition from the classical parietal response of other species and the histamine response in the horse (See Chap.2), but also by the ability of pyrilamine to inhibit a maximal acid response.

CHAPTER 4  
PLACEMENT OF A CATHETER FOR COLLECTION OF DUODENAL CONTENTS  
IN HORSES WITH CHRONIC GASTRIC CANNULAS AND ITS EFFECT ON  
GASTRIC SECRETION

Introduction

The contents of various parts of the gastrointestinal system differ in chemical and physical characteristics between location and species. Much of the normal gastrointestinal function of the individual species relates to the anatomy of their alimentary system and the type of diet which they consume. Increasing our understanding the normal function is often complicated by those same differences. Equine gastric secretion and the composition of the contents under various conditions have been studied by numerous investigators utilizing several techniques.<sup>31,44,48-54</sup> The development of a chronic gastric cannula<sup>31</sup> for collection of gastric contents has added greatly to the knowledge regarding equine gastric physiology.

Study of the function of the equine proximal duodenum, biliary system, and pancreas has been even more difficult due to an anatomical location which strictly limits surgical exposure.<sup>87,88</sup> Up to now, attempts to study the proximal duodenum and associated structures have met with serious difficulties and been basically unsuccessful in providing additional information on the physiology of this region.

The reflux of duodenal contents into the empty equine stomach has been observed during endoscopic gastric examination even when there is no evidence of underlying pathology.<sup>50,51</sup> The importance, frequency and volume of reflux have not been evaluated. Nor has the composition of the duodenal contents which are mixing with the gastric contents been fully analyzed. Reflux of large volumes of small intestinal contents into the stomach is reported during various disease conditions such as anterior enteritis and small intestinal obstruction.<sup>89,90</sup>

The presence of chronic indwelling gastric cannulas in research horses has made access to the duodenum much easier for investigator and animal. This study describes how, with the aid of an endoscope passed up through a gastric cannula, a catheter can be placed into the equine duodenum for the

collection of fluid. The two objectives of this study were to determine the composition of the duodenal fluid and whether the presence of the catheter passing into the duodenum had an effect on the gastric contents collected from the cannula before and during stimulation of secretion with pentagastrin.

### Materials and Methods

#### Horses

Five Thoroughbreds(TB), two mixed breed (MB) horses, and one Arabian (AR) [3 mares, 5 geldings] between 3 and 20 years in age, were used in these studies. (TABLE 5) For

TABLE 5.  
Horses used in Gastric Collection Studies.

| ID | AGE  | BREED | SEX |
|----|------|-------|-----|
| B  | 5 Y  | ARAB  | G   |
| D  | 7 Y  | TB    | G   |
| E  | 20 Y | TB    | M   |
| H  | 5 Y  | TB    | G   |
| I  | 6 Y  | TB    | M   |
| J  | 3 Y  | MIXED | G   |
| M  | 7 Y  | MIXED | M   |
| T  | 5 Y  | TB    | G   |

both catheter studies, six of the horses (5TB,1AR) were selected. The no catheter/pentagastrin study was performed on four (2MB,1AR,1TB) horses. Two horses (1TB,1AR) were involved in both studies. (TABLE 6) The horses were all healthy and ranged in weight from 430 to 510 kg. They were maintained on grass pasture and provided coastal hay ad lib and 12% protein grain twice daily. All horses were dewormed every 2 months, vaccinated for encephalomyelitis/tetanus every 6 months and were free of clinical signs of gastrointestinal disease. A chronic indwelling gastric cannula as described by Campbell-Thompson and Merritt<sup>31</sup> had

TABLE 6.  
Descriptions and Abbreviations for Each Study.

| EXPERIMENT<br>ABBREVIATION | INFUSION<br>(secretagogue) | CATHETER<br>(via cannula) | HORSES USED |
|----------------------------|----------------------------|---------------------------|-------------|
| PG/NOC                     | Pentagastrin               | None                      | B,E,J,M     |
| PG/CATH                    | Pentagastrin               | Intraduodenal             | B,D,E,H,I,T |

been prepared in these horses 1 to 24 months prior to this study. All studies were approved by the University of Florida IACUC.

### Experimental preparation

Experiments were performed with no less than a one week interval between them. The horses were fasted with free choice water for 20 hours prior to an experiment. They were loosely restrained in the laboratory for the entire experiment. The gastric cannula was opened and allowed to drain by gravity for 15 to 20 minutes while a indwelling jugular catheter was emplaced. For the catheter studies, a video endoscope (WelchAllyn, Skaneateles Fall, NY) was inserted through the gastric cannula into the stomach and steered into the duodenum to a point approximately 30 cm past the area of the duodenal diverticulum. A 4.5m long stylet was threaded through the biopsy port of the endoscope until it was seen passing from the distal end of the scope. The endoscope was slowly withdrawn as the stylet was threaded through the biopsy port, watching that it stayed in place as the scope was removed. The distance from the pylorus to the end of the gastric cannula was noted. The presence of the stylet passing through the pylorus was visually confirmed prior to removing the endoscope from the cannula. The stylet was marked at the end of the cannula, after which a specially modified stallion urinary catheter

(see below) was passed over it. The mark on the stylet was used to assure that it remained in position as the catheter was introduced through the cannula into the stomach, then through the pylorus and into the duodenum. The stylet was left in place until catheter placement was believed to be complete. The completed setup (fig. 4) resulted in the

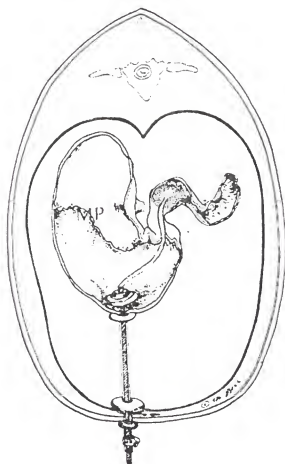


**Figure 4** Cross sectional view of duodenal catheter passing through the gastric cannula into the stomach and entering the proximal duodenum.

ability to collect gastric contents from the cannula and duodenal contents from the catheter into separate containers. The fluids were collected into 1L fluid bags suspended from a surcingle. The cannula and catheter were both allowed to drain by gravity for 15 minutes after completion of catheter placement. In the studies where there was no intraduodenal catheter (NOC) in place, gastric contents only were collected by gravity into 1L fluid bags.

#### Catheter Design

The specialized catheter was fashioned from a 137 cm stallion urinary catheter (Jorgensen Laboratories, Inc., Loveland, Co). (fig.5) Its end was opened to allow free passage of the stylet and several additional 5mm side holes were placed in the 15cm closest to the tip. It was distinctly marked at 20 cm from the tip and this mark was considered the "0cm" mark. Additional marks were made every 5cm markings from that point to the end. To fix the catheter in position, a 10cm section of silastic tubing [16mm I.D.] was placed over a 5cm section of the barrel of a 12ml syringe (Monoject, St. Louis, MO.) and the catheter

passed tightly through the wall of the silastic tubing into the lumen and out through the syringe barrel lumen.

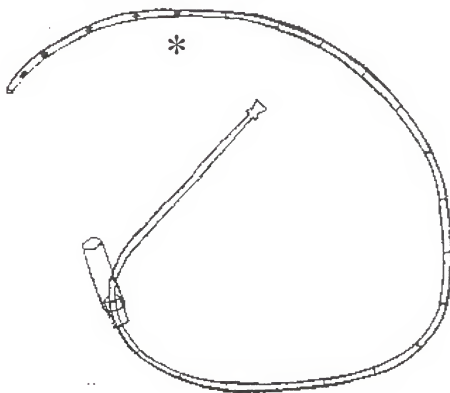


**Figure 5** Specialized catheter for collection of duodenal contents. The bold mark is signified by \* and is located 20 cm from tip. Multiple fenestrations within that 20 cm region of the catheter.

One end of the syringe barrel locked into the end of the silastic gastric cannula and the other was attached to the short segment of silastic tubing which locked the catheter in a fixed position. The long stylet was made by joining together 3 stylets provided with stallion catheters. The

catheter was passed until the bold mark [0cm] was 5cm aborad to the pylorus.

#### Experimental protocol

Gastric (in all studies) and duodenal contents (only in the "catheter" studies [CATH]) were collected in 15 minute aliquots. Gastric samples were filtered through gauze prior to analysis. Volume of both gastric and duodenal collections was measured and, if available, a 50 ml sample was saved for sample analyses. Analyses were performed either immediately or samples were frozen for later analysis. Each experiment lasted 3 hours. During the first 45 minutes [basal collection], no treatment was given. Beginning at time  $t=45\text{min}$ , pyrilamine maleate (Histavet-P, Schering-Plough NJ) was infused IV at 1 mg/kg over a 15 minute period. No additional treatments were given for 30 minutes. At time  $t=90\text{min}$ , an IV infusion of pentagastrin [6  $\mu\text{g/kg-hr}$ ] was administered by infusion pump (Harvard Apparatus, South Natick MA) and continued for the remainder of the experiment. At the conclusion of the catheter

experiments, the catheter position was rechecked before the catheter was withdrawn, and the cannula closed.

Each infusion was given in a volume of 60 mls/hr. Crystalline pentagastrin (Sigma Chemical Co., St. Louis MO) was prepared by dissolving with 0.8 ml of DMSO and 90 mls of 0.9% NaCl before filtering through a 0.22  $\mu$ m cellulose nitrate filter (Corning, Corning NY) in preparation for infusion.

#### Sample analysis

Gastric and duodenal sample volume was measured in a graduated cylinder and then an aliquot was analyzed immediately for chloride ion concentration. Gastric samples were also analyzed immediately for hydrogen ion concentration. Duodenal samples were kept in an ice bath until they were analyzed for bicarbonate ion concentration. Both gastric and duodenal samples were frozen for later measurement of sodium and potassium ion concentration.

Using a automatic titrator (Radiometer, Copenhagen Denmark), hydrogen ion concentration was measured in duplicate by titration with 0.1N NaOH to an endpoint of 7.4.

Chloride ion concentration was measured in duplicate by a digital chloridometer (Buchler Instruments Div., Nuclear Chicago, Fort Lee NJ) with acid reagent (Labconco, Kansas City, Mo). Chloride standard (Labconco, Kansas City, Mo) was used to calibrate the machine prior to each experiment and after every 20 tests. Bicarbonate ion concentration was determined by back-titration method of Isenberg et al.<sup>91</sup> with the automatic titrator (Radiometer, Copenhagen Denmark) using 0.1N NaOH to titrate to an endpoint of 8.4. Sample solutions were gassed with nitrogen washed in barium hydroxide to remove carbon dioxide prior to and during the titration and were analyzed in triplicate. Standard solutions prepared in laboratory were measured in quadruplicate prior to each experiment. Sodium and potassium ion concentration were measured by flame photometry (Instrumentation Laboratories Inc., Lexington MA) on samples which had been frozen at -20°C. Samples were thawed to room temperature, and diluted in an internal standard lithium solution (Dilumat, Fisher Scientific). The machine was calibrated with known  $[Na^+]/[K^+]$  standards (Instrumentation Laboratories Inc., Lexington MA) prior to any analyses and after every 5 samples.

### Analysis of data

For the purpose of this paper, duodenal contents were analyzed to determine electrolyte concentration ranges, but these data were not statistically evaluated. Statistical analysis was performed on volume, acid concentration, acid output, sodium concentration, and sodium output from the gastric samples. Output was calculated on a per kg body weight basis from the volume and hydrogen or sodium ion concentration and was expressed as  $\mu\text{Eq/kg-15min}$ . The last 30 minutes of basal collections, post-pyrilamine collections, and the first and last 30 minutes of infusion-related collections were compared between studies. A two-way ANOVA was performed for factors of time (basal, post-pyrilamine, early infusion, and late infusion), and duodenal catheter (yes or no) and interactions of these factors. A  $p < 0.05$  was considered significant and all pairwise multiple comparisons by Tukey test were performed.

## Results

### Gastric Contents

Volume. (Table 7) The volume of gastric collection differed significantly ( $p < 0.01$ ) between the designated time blocks. The volume was significantly greater ( $p < 0.05$ ) during the late infusion block than during all other blocks. The early infusion volume was significantly greater ( $p < 0.05$ ) than the post-pyrimidine volume, but did not differ significantly from the basal volumes. The basal and post-pyrimidine volumes did not differ significantly. The volumes collected during the CATH study were significantly ( $p < 0.01$ ) greater than during the NOC study. There was no significant interaction between time blocks and catheter status.

Acid Concentration. (Table 7) Acid concentration varied significantly ( $p = 0.001$ ) among the time blocks with a significantly higher ( $p < 0.05$ ) concentration during late infusion. The  $[H^+]$  was not significantly different between basal, post-pyrimidine and early infusion blocks. The NOC study had a significantly ( $p = 0.016$ ) higher concentration of

acid than the CATH study. No significant interactions were found between time blocks and catheter.

TABLE 7.  
Data from Study With and Without Duodenal Catheter During  
Pentagastrin Stimulation (Mean and SEM's)

|                                            | STUDY | BASAL               | PYRILAMINE          | EARLY                                | LATE                             |
|--------------------------------------------|-------|---------------------|---------------------|--------------------------------------|----------------------------------|
| VOLUME<br>(ml/15<br>min)                   | NOC   | 287.5 $\pm$<br>28.0 | 171.3 $\pm$<br>27.0 | 405.0 $\pm$<br>125.4 $\blacklozenge$ | 568.8 $\pm$<br>83.4 $\star$      |
|                                            | CATH* | 541.7 $\pm$<br>29.7 | 396.6 $\pm$<br>32.1 | 653.3 $\pm$<br>66.0 $\blacklozenge$  | 885.8 $\pm$<br>26.7 $\star$      |
| [H <sup>+</sup> ]<br>(mEq/L)               | NOC** | 39.5 $\pm$<br>6.1   | 32.3 $\pm$ 5.2      | 31.9 $\pm$<br>10.0                   | 52.4 $\pm$<br>9.4 $\star$        |
|                                            | CATH  | 26.5 $\pm$<br>4.1   | 28.9 $\pm$ 3.3      | 20.4 $\pm$<br>3.7                    | 42.4 $\pm$<br>2.2 $\star$        |
| ACID<br>OUTPUT<br>( $\mu$ Eq/kg-<br>15min) | NOC   | 24.5 $\pm$<br>3.9   | 12.1 $\pm$ 1.9      | 22.5 $\pm$<br>6.5                    | 57.4 $\pm$<br>3.8 $\star$        |
|                                            | CATH* | 31.9 $\pm$<br>6.2   | 24.9 $\pm$ 3.7      | 30.2 $\pm$<br>6.8                    | 80.2 $\pm$<br>4.9 $\star$        |
| [Na <sup>+</sup> ]<br>(mEq/L)              | NOC   | 106.1 $\pm$<br>6.1  | 110.8 $\pm$<br>5.7  | 108.3 $\pm$<br>10.0                  | 93.4 $\pm$<br>8.2 $\blacksquare$ |
|                                            | CATH  | 106.8 $\pm$<br>6.0  | 104.4 $\pm$<br>3.3  | 107.4 $\pm$<br>4.2                   | 88.2 $\pm$<br>3.3 $\blacksquare$ |
| NA<br>OUTPUT<br>( $\mu$ Eq/kg-<br>15min)   | NOC   | 72.5 $\pm$<br>10.0  | 44.8 $\pm$ 8.5      | 107.3 $\pm$<br>40.0 $\blacklozenge$  | 133.8 $\pm$<br>29.2 $\bullet$    |
|                                            | CATH* | 122.1 $\pm$<br>8.4  | 88.0 $\pm$ 8.0      | 146.4 $\pm$<br>13.6 $\blacklozenge$  | 167.5 $\pm$<br>9.9 $\bullet$     |

\* Significantly greater than NOC

\*\* Significantly greater than CATH

$\star$  Significantly greater than all other time blocks

$\blacklozenge$  Significantly greater than post-pyrimilamine time block

$\blacksquare$  Significantly less than all other time blocks

$\bullet$  Significantly greater than basal & post-pyrimilamine time blocks

Acid Output. (Table 7) The output of acid decreased after the pyrilamine infusion and increased during pentagastrin infusion. These changes in acid output over time differed significantly ( $p < 0.001$ ). Acid output (AO) was significantly greater ( $p < 0.05$ ) during late infusion than during all other periods, however, the differences between outputs during each of the other times did not differ significantly. The AO was significantly greater ( $p = 0.001$ ) during the CATH study than the NOC study.

Sodium Concentration. (Table 7) The  $[Na^+]$  was relatively constant until the late infusion block during which time the concentration decreased significantly ( $p = 0.01$ ). There was no significant difference in the concentration between CATH and NOC studies.

Sodium Output. (Table 7) There was a significant ( $p < 0.001$ ) effect of time on sodium output. The output during late infusion was significantly greater ( $p < 0.05$ ) than during basal or post-pyrilamine periods, but not significantly greater than during the early infusion period. Early infusion sodium output was also significantly greater than post-pyrilamine, though it was not significantly

greater than the basal output. The output during the CATH study was significantly greater ( $p=0.001$ ) than during the NOC study.

### Duodenal Contents

Duodenal fluid was generally thick and mucoid and tended to be dark yellow to green, in color. The bicarbonate ion concentration ranged between 19-40 mEq/L;

TABLE 8.  
Electrolyte Composition of Fluid from Duodenal Catheter  
During Basal, Post-Pyrimidine, and Pentagastrin Infusion  
Collection Periods. [Mean  $\pm$  SEM]

| DUODENAL                       | BASAL           | PYRILAMINE      | INFUSION        |
|--------------------------------|-----------------|-----------------|-----------------|
| [HCO <sub>3</sub> ]<br>(mEq/L) | 23.2 $\pm$ 2.6  | 16.2 $\pm$ 1.5  | 33.0 $\pm$ 2.3  |
| [Na <sup>+</sup> ]<br>(mEq/L)  | 147.5 $\pm$ 3.9 | 151.5 $\pm$ 6.7 | 144.9 $\pm$ 2.4 |
| [K <sup>+</sup> ]<br>(mEq/L)   | 4.5 $\pm$ 0.2   | 4.4 $\pm$ 0.3   | 3.6 $\pm$ 0.1   |
| [Cl <sup>-</sup> ]<br>(mEq/L)  | 118.1 $\pm$ 5.5 | 119.6 $\pm$ 5.2 | 115.1 $\pm$ 6.1 |

it decreased noticeably in the post-pyrimidine collections and was increased during pentagastrin infusion. The fluid had a high concentration of sodium (120-190 mEq/L) and low concentration of potassium (2.4-5.5 mEq/L) compared to that of gastric contents, in which the [Na<sup>+</sup>] ranged between 25-

125 mEq/L and  $[K^+]$  between 6-20 mEq/L. Chloride ion concentrations were in the range of 95-160 mEq/L, whereas the gastric contents had  $[Cl^-]$  ranging from 130 to 180 mEq/L. The mean concentrations of sodium, potassium, and chloride were consistent throughout the experiment.

### Discussion

The placement of a duodenal catheter through the gastric cannula required variable amounts of manipulation of the videoendoscope. The time required for introduction of the video endoscope into the duodenum and passage of the stylet and threading of the catheter ranged from 10 to 25 minutes. The differences related in position of the pylorus relative to the cannula and the dexterity of the investigator on that day. The horses did not appear to be bothered by the process nor by the presence of the catheter during the experiments. Catheter experiments proceeded as the no catheter experiments did. Gastric contents were easily collected from the cannula even with the catheter in place. During some time periods, no fluid was collected from the duodenal catheter. However, this did not indicate

blockage as fluid was collected during the next time period as patency was checked injection of air through the catheter.

In the catheter experiments, gastric contents had significantly greater volume, acid output, and sodium output as well as a significantly lower  $[H^+]$ . The presence of the catheter passing through the pylorus may have allowed additional fluid reflux from the duodenum into the stomach. This may have occurred due to capillary action along the catheter or by preventing complete closure of the pylorus. The duodenal fluid had a high concentration of sodium and reflux of this fluid may account for increased sodium output and volume of gastric contents in CATH experiments. The acid response to pentagastrin with the duodenal catheter was similar to previous studies in the horse;<sup>31,44</sup> however, during pentagastrin stimulation, the gastric contents  $[H^+]$  in the CATH study was less than in the NOC study. We suggest that this may have been due to dilution of the gastric secretions by the fluid refluxing from the duodenum around the catheter.

The increased acid output observed in the CATH study was not related to the reflux of duodenal fluid. The post-

pyrilamine period decrease in acid output in the CATH study was not as dramatic in the NOC study. The increasing acid output during the early and late infusion periods of the CATH were closer to the normal pentagastrin response observed in horses without pyrilamine pretreatment (See Chap.3) than to an unusually profound response to pyrilamine in the NOC study. Decreased maximal acid output in horses stimulated with pentagastrin following the administration of pyrilamine maleate may be due to decreased mucosal blood flow. (See Chap. 3) The placement of the duodenal catheter may also potentiate gastric acid secretion by mechanical stimulation<sup>2,3,8,17,18</sup> in the gastric antrum resulting in the local release of gastrin or acetylcholine, thereby lessening the effect of the pyrilamine. In humans and dogs, distention of the antral region has been shown to augment histamine or gastrin- related secretion of acid.<sup>2,3,18</sup> Although the catheter was not large and did not distend the antrum, it did contact the gastric mucosa and may have stimulated local intramural reflexes<sup>2,3,17,18</sup> involved in the secretory response.

Sodium output increased dramatically during pentagastrin infusion in both the CATH and NOC studies,

although, the output was significantly greater in the CATH studies. The infusion related increase in sodium output was consistent with the apparently equine specific response to pentagastrin.<sup>31,44,51</sup> Monitoring of sodium ions in the stomach has been used to assess duodenogastric reflux in humans.<sup>92,93</sup> The sodium rich fluid collected from the equine gastric cannulas is probably of duodenal origin<sup>50,51</sup> and the reflux of this sodium rich duodenal fluid around the duodenal catheter could explain the increased sodium output during the CATH study.

The equine gastric cannula model has been beneficial in the understanding of equine gastric physiology and the development pharmaceuticals for the treatment of gastric ulcers.<sup>31,49,53,54</sup> It appears that this model may also allow further investigation of equine gastric and small intestinal physiology. The duodenal contents had a high concentration of sodium and chloride and low concentration of potassium and is most likely the fluid which dilutes parietal secretions during gastric collections. The passage of a duodenal catheter and collection of duodenal contents does not prevent normal acid stimulation in response to pentagastrin, but may enhance reflux of duodenal contents into the stomach.

CHAPTER 5  
THE EFFECT OF PYLORIC OBSTRUCTION ON EQUINE BASAL AND  
STIMULATED GASTRIC SECRETION

Introduction

In horses, the maximal secretory response to pentagastrin (PG) comprises a large volume of sodium-rich fluid of relatively low acidity ( $[H^+]$  (40-60 mEq/l).<sup>31,44,49,51</sup> This is different from other monogastric species that have been studied, where the gastric contents under maximal PG stimulation have high  $H^+$  and low  $Na^+$  concentrations, comparable to that seen in response to histamine stimulation.<sup>30,37-42</sup> On the other hand, the acid and sodium concentrations of equine gastric contents under maximal histamine stimulation are similar to those seen in other monogastric species in that the  $[H^+]$  ranges between 80-110 mEq/l and the  $[Na^+]$  is relatively low. (See Chap.2) The maximal acid output (MAO) was equivalent to that during pentagastrin infusion, however, the sodium outputs differed greatly. In other monogastric species, the difference

between histamine and pentagastrin stimulation is the relative sensitivity to each, rather than the composition of the resultant secretions.<sup>17,28,30</sup>

Furthermore, when PG-induced gastric acid secretion of horses is inhibited by either a histamine-2 receptor antagonist or a proton pump blocking agent, a large volume of basic, sodium-rich fluid can still be collected from the stomach.<sup>31,49,51,53,54</sup> This is also distinctly different from the response in other monogastrics, where inhibition of acid secretion results in coincident reduction in the volume of gastric contents.<sup>37,94</sup> Whether the origin of this fluid is primarily gastric or extragastric in origin has not been identified. The objective of this study was to determine more exactly the source of this large "nonparietal" component of equine gastric contents that is seen in response to PG stimulation.

### Materials and Methods

#### Horses

Five Thoroughbreds and one Arabian [2 mares, 4 geldings] ranging from 3 to 20 years were used in this

study. The horses were all healthy and weighed between 430 and 510 kg. They were maintained on grass pasture and provided coastal hay free choice, and 12% protein grain twice daily. They were dewormed every 2 months, vaccinated for encephalomyelitis and tetanus every 6 months and were free of clinical signs of any disease. Chronic indwelling gastric cannulas as described by Campbell-Thompson and Merritt<sup>31</sup> had been prepared in these horses from 1 to 24 months prior to this study. All studies were approved by the University of Florida IACUC.

#### Experimental protocol

Horses were fasted with free choice water for 20 hours prior to an experiment. Experiments were performed with no less than a one week interval between them. The horses were loosely restrained in the laboratory for the entire experiment. The gastric cannula was opened and allowed to drain by gravity for 15 to 20 minutes, while a indwelling jugular catheter(Abbocath) was emplaced. Videoendoscopy was used to place a specially designed catheter into the duodenum, as described by Kitchen et al.(See Chap. 4) The catheter was further adapted in half of the experiments by

the addition of an inflatable balloon, which could be inflated or deflated by a three-way stopcock near the proximal end of the catheter. (fig. 6) The catheter was passed until a predetermined mark or the balloon was 5cm

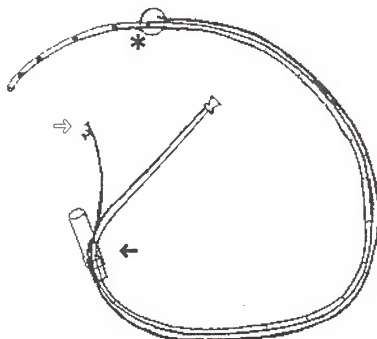


**Figure 6** Specialized Balloon catheter. \* at balloon which is 20 cm from the end of the catheter. ⇒ marks the 3-way stopcock and tubing to fill balloon. ← points to the silastic tube which keeps the catheter fixed in place and allows collection of gastric contents.

aborad to the pylorus. The balloon was inflated with a 60 ml syringe until firm resistance was felt. The catheter was gently pulled to verify its placement was fixed by the balloon. The completed setup (fig. 7) resulted in the

ability to collect gastric contents from the cannula and duodenal contents from the catheter into separate containers, which were 1L size bags suspended from a surcingle. The cannula and catheter were both allowed to

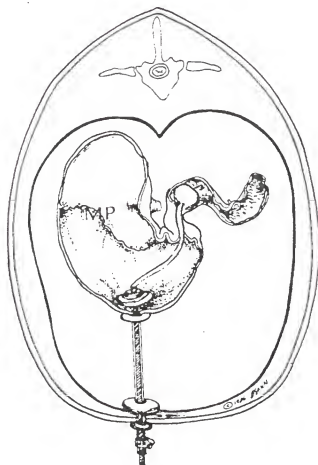


**Figure 7** Cross sectional view showing balloon catheter positioned in the proximal duodenum through the gastric cannula.

drain by gravity for 15 minutes after completion of catheter placement and inflation of balloon in those experiments with pyloric obstruction.

Gastric and duodenal contents were continuously collected by gravity drainage, separately. The containers were switched every fifteen minutes and samples from each time block were analyzed. Gastric samples were filtered through gauze prior to analysis. Volume of both gastric and duodenal collections was measured and if available, a 50 ml aliquot was saved for sample analyses. Analyses were performed either immediately or samples were frozen for later analysis. Each experiment lasted 3 hours. The design was a 6x6 Latin square repeated measures design randomized for treatment. (See Table 9.) Three different IV infusions

Table 9.  
EXPERIMENTAL DESIGN

| INFUSION     | CATHETER TYPE | ABBREVIATION |
|--------------|---------------|--------------|
| Saline       | No Balloon    | SAL/NB       |
| Histamine    | No Balloon    | HIST/NB      |
| Pentagastrin | No Balloon    | PG/NB        |
| Saline       | Balloon       | SAL/B        |
| Histamine    | Balloon       | HIST/B       |
| Pentagastrin | Balloon       | PG/B         |

No Balloon = Pylorus Not Obstructed

Balloon = Pylorus Obstructed

were given, with the duodenal catheter in place, either with or without an inflated pyloric balloon. During the

first 45 minutes [basal collection], no treatment was given. Beginning at time  $t=45\text{min}$ , pyrilamine maleate (Histavet-P, Schering-Plough NJ) was infused IV at  $1\text{ mg/kg}$  over a 15 minute period. No additional treatments were given for 30 minutes. At time  $t=90\text{min}$ , an IV infusion of either 0.9% saline [ $60\text{ mls/hr}$ ], histamine [ $30\text{ }\mu\text{g/kg-hr}$ ], or pentagastrin [ $6\text{ }\mu\text{g/kg-hr}$ ] was administered by infusion pump (Harvard Apparatus, South Natick MA) and continued for the remainder of the experiment. Infusions were prepared as previously described. (See Chap. 4) At the conclusion of the experiment, the intraduodenal catheter position was rechecked before it was withdrawn, and the cannula closed.

#### Sample analysis

Volume was measured in a graduated cylinder and aliquots were analyzed immediately for pH, and chloride ion concentration. Gastric samples were analyzed immediately for hydrogen ion concentration. Duodenal samples were kept in an ice bath until they were analyzed for bicarbonate ion concentration. Both gastric and duodenal samples were frozen for later analysis of sodium and potassium ion concentration. Gastric samples from  $t=45\text{min}$  were analyzed

for bile acids to verify complete occlusion of the pylorus by the balloon in those experiments.

The pH was determined by glass electrode (Radiometer, Copenhagen Denmark) calibrated at 20°C using commercial buffer solutions of pH 2 and 7 (pH standard, Fischer Scientific). Using an automatic titrator (Radiometer, Copenhagen Denmark), hydrogen ion concentration was measured in duplicate by titration with 0.1N NaOH to an endpoint of 7.4. Chloride ion concentration was measured in duplicate by a digital chloridometer (Buchler Instruments Div., Nuclear Chicago, Fort Lee NJ) with acid reagent (Labconco, Kansas City, Mo). Chloride standard (Labconco, Kansas City, Mo) was used to calibrate the machine prior to each experiment and after every 20 tests. Bicarbonate ion concentration was determined by back-titration method of Isenberg et al.<sup>91</sup> with the automatic titrator (Radiometer, Copenhagen Denmark) using 0.1N NaOH to titrate to an endpoint of 8.4. Sample aliquots were gassed with nitrogen washed in barium hydroxide to remove carbon dioxide prior to and during the titration. Bicarbonate measurements were done in triplicate, and standard solutions prepared in laboratory were measured in quadruplicate prior to each experiment. Sodium and potassium ion concentration were

measured in duplicate by flame photometry (Instrumentation Laboratories Inc., Lexington MA) on samples which had been frozen at  $-20^{\circ}\text{C}$ . Samples were thawed to room temperature and were mixed and diluted in an internal standard lithium solution (Dilumat, Fischer Scientific), prior to analysis. The machine was calibrated with known  $[\text{Na}^+]/[\text{K}^+]$  standards (Instrumentation Laboratories Inc., Lexington MA) prior to analysis and after every 5 samples. Bile acid concentration was determined by an enzymatic, colourimetric test kit (Enzabile, Nycomed, Norway) in the VMTH Clinical Pathology Laboratory.

#### Analysis of data

A complete randomized block design experiment was used. The treatment order was randomized for each horse. In order to obtain basal samples and pretreat all horses with pyrilamine maleate, the first 90 minutes of each experiment was the same. For statistical analysis and descriptive purposes, the results from the  $t=30$  and  $45$  min were averaged and are referred to as "R1". The results from collection following pyrilamine maleate infusion ( $t=75$  &  $90\text{min}$ ) were averaged and labeled "R2". The three "R1" values from

experiments without pyloric obstruction and the three "R1" values from experiments with pyloric obstruction were averaged to derive "basal" means. The "R2" values were also averaged to derive two "pyrilamine" means. The first six aliquots were grouped as "pre" and the next six aliquots were grouped as "post" treatment. All outputs were calculated on a per kg body weight basis from the volume and ion concentrations and were expressed as  $\mu\text{Eq/kg/15min}$ . Volume, pH, electrolyte ion concentration, and electrolyte ion output data were analyzed by ANOVA for repeated measures. Differences between drug effects, drug\*time interaction, time, drug\*balloon interaction, balloon, balloon\*time interaction and drug\*balloon\*time interaction were analyzed. Least significant difference was used for pairwise comparison of means. Significance was chosen as  $p \leq 0.05$ .

### Results

The horses maintained their bodyweight or gained weight during the course of the study, and they did not appear to be painful or anxious during the experiments. They stood quietly in the lab throughout and behaved similarly with or

without pyloric obstruction. The duodenal mucosa appeared healthy in all studies and no changes were observed in the area where the inflated balloon was positioned. No colics were observed in these horses during or after these studies. Rarely, a small piece of mucosa would pass from the duodenal catheter. The size of these pieces was consistent with the holes in the catheter and may have occurred by suction of the catheter onto the mucosa. No residual scarring was visible endoscopically.

#### Pre-infusion

#### Gastric samples

(See Table 10,11,12,13,14)

The gastric samples collected after inflation of the balloon to obstruct the pylorus were clear and watery, although clear mucus and white foam was sometimes present in the collection. Gastric samples collected with the duodenal catheter and no obstruction of the pylorus were yellow to greenish-yellow and cloudy as observed in other gastric cannula studies.<sup>31,44</sup> Time was statistically significant in most parameters measured and related to the administration of pyrilamine maleate. The time effect was significant ( $p < 0.05$ ) for all parameters except chloride ion

concentration, and was consistent between treatment groups. After treatment with pyrilamine maleate, the collection volume ( $p=0.0001$ ), acid concentration ( $p=0.0001$ ), acid output ( $p=0.0001$ ), sodium output ( $p=0.0001$ ), potassium concentration ( $p=0.0001$ ), potassium output ( $p=0.0001$ ), and chloride output ( $p=0.0001$ ) were decreased significantly, while pH ( $p=0.0457$ ) and sodium concentration ( $p=0.0001$ ) significantly increased. The balloon [obstruction vs. no obstruction of the pylorus] affected all parameters, except pH,  $[Na^+]$ , and  $[K^+]$ . The experiments with the balloon had significantly lower volume ( $p<0.00001$ ), and acid ( $p=0.02517$ ), sodium ( $p<0.00001$ ), potassium ( $p<0.00001$ ), and chloride ( $p<0.00001$ ) outputs than those without balloon. Acid ( $p=0.02075$ ) and chloride ( $p=0.00102$ ) concentrations were significantly higher in the experiments with pyloric obstruction. As expected, no significant differences were found between groups with regard to which infusion was to be given. Therefore, two "basal" and "pyrilamine" values were calculated from mean of the "R1" and "R2" of either experiments with balloon, or experiments without balloon.

## Post-infusion

### Gastric samples

Volume. (Table 10) After starting infusion, the volume of gastric collections increased significantly ( $p=0.0001$ ) through the time course ( $t=105$  to  $180$ ). A significant drug\*time interaction was observed ( $p=0.0001$ ). Pentagastrin experiments resulted in a rapid, marked increase that was significantly greater than saline ( $p=0.0001$ ), but not significantly greater than the increase with histamine, which was also significantly greater than saline ( $p=0.0003$ ). The balloon\*time interaction was also significant ( $p=0.0214$ ), since the relative volume increase was greater in the studies with pyloric obstruction than in those with no obstruction. In all infusions, the volume of gastric contents collected was significantly greater ( $p<0.00001$ ) with no balloon. The drug effect was also highly significant ( $p<0.00001$ ). Specifically, pentagastrin induced volumes significantly greater than saline ( $p<0.00001$ ) and histamine ( $p=0.00001$ ), and histamine volumes were also significantly greater than saline ( $p=0.00003$ ). There was a significant ( $p=0.04437$ ) drug\*balloon

interaction. Further comparison demonstrated the following gastric volume differences: PG/NB was significantly greater than HIST/NB ( $p < 0.00001$ ) or SAL/NB ( $p < 0.00001$ ), HIST/NB was significantly greater than SAL/NB ( $p = 0.00178$ ), PG/B was significantly greater than HIST/B ( $p = 0.04694$ ) or SAL/B ( $p < 0.00001$ ), and HIST/B was significantly greater than SAL/B ( $p = 0.00154$ ).

Table 10.  
VOLUME AND pH OF GASTRIC CONTENTS  
Mean  $\pm$  SEM

|                    | B/NB | BASAL            | PYRILAMINE       | INFUSIONS (max) |                  |
|--------------------|------|------------------|------------------|-----------------|------------------|
| VOLUME<br>ml/15min |      |                  |                  | SAL *           | 472.9 $\pm$ 30.5 |
|                    | NB   | 466.1 $\pm$ 58.4 | 361.6 $\pm$ 51.1 | HIST *          | 664.2 $\pm$ 51.5 |
|                    |      |                  | +                | PG *            | 885.8 $\pm$ 39.5 |
| VOLUME<br>ml/15min |      |                  |                  | SAL *           | 226.9 $\pm$ 42.5 |
|                    | B♦   | 251.0 $\pm$ 48.9 | 153.9 $\pm$ 30.1 | HIST *          | 445.5 $\pm$ 56.0 |
|                    |      |                  | +                | PG *            | 523.8 $\pm$ 52.4 |
| pH                 |      |                  |                  | SAL             | 2.45 $\pm$ 0.70  |
|                    | NB   | 2.10 $\pm$ 0.48  | 2.43 $\pm$ 0.64  | HIST §          | 1.33 $\pm$ 0.07  |
|                    |      |                  | +                | PG              | 1.59 $\pm$ 0.05  |
| pH                 |      |                  |                  | SAL             | 2.45 $\pm$ 0.91  |
|                    | B    | 1.95 $\pm$ 0.41  | 2.64 $\pm$ 0.85  | HIST §          | 1.21 $\pm$ 0.04  |
|                    |      |                  | +                | PG              | 1.27 $\pm$ 0.02  |

\* Response to this infusion significantly different ( $p < 0.05$ ) from responses to other infusions

♦ B significantly different ( $p < 0.05$ ) from NB

§ HIST significantly less ( $p < 0.05$ ) than other infusions

+ Pyrilamine significantly different than other time blocks

pH. (Table 10) The only significant effect on pH ( $p=0.02600$ ) was related to the drug of infusion. Histamine infusion resulted in pH significantly lower than saline ( $p=0.00866$ ), but not significantly different from pentagastrin.

Potassium ion concentration (Table 11) The concentration of potassium ion increased significantly ( $p=0.0001$ ) after initiation of the infusions. The drug\*time interaction was also significant ( $p=0.0001$ ). Histamine infusion rapidly resulted in  $[K^+]$  significantly greater than pentagastrin ( $p=0.0029$ ) or saline ( $p=0.0001$ ). Time-related changes in  $[K^+]$  did not differ significantly between pentagastrin and saline infusions. The  $[K^+]$  was significantly greater ( $p=0.00004$ ) in experiments with the balloon than in no balloon experiments. There was a significant ( $p<0.00001$ ) drug effect. The  $[K^+]$  during histamine infusion was significantly greater than during pentagastrin ( $p=0.00007$ ) or saline ( $p<0.00001$ ) infusion, and the pentagastrin induced  $[K^+]$  was significantly greater than that of saline ( $p=0.00168$ ). The drug\*balloon interaction was significant ( $p=0.01112$ ) with the following specific concentration differences: HIST/NB was significantly

greater than SAL/NB ( $p=0.00023$ ) and PG/NB ( $p=0.00039$ ), HIST/B was significantly greater than SAL/B ( $p<0.00001$ ) and PG/B ( $p=0.01767$ ), and PG/B was significantly greater than SAL/B ( $p=0.00006$ ).

Table 11.  
POTASSIUM IN GASTRIC CONTENTS  
Mean  $\pm$  SEM

|                                                    | B/NB | BASAL           | PYRILAMINE     | INFUSIONS (max) |                 |
|----------------------------------------------------|------|-----------------|----------------|-----------------|-----------------|
| [K <sup>+</sup> ]<br>mEq/L                         |      |                 |                | SAL             | 9.8 $\pm$ 0.64  |
|                                                    | NB   | 9.8 $\pm$ 0.92  | 8.1 $\pm$ 0.64 | HIST *          | 14.0 $\pm$ 0.90 |
|                                                    |      |                 | +              | PG              | 10.3 $\pm$ 0.53 |
| [K <sup>+</sup> ]<br>mEq/L                         |      |                 |                | SAL *♦          | 9.4 $\pm$ 0.77  |
|                                                    | B    | 10.3 $\pm$ 1.18 | 8.0 $\pm$ 0.67 | HIST*♦          | 17.7 $\pm$ 1.03 |
|                                                    |      |                 | +              | PG ♦♦           | 14.2 $\pm$ 0.94 |
| K <sup>+</sup><br>OUTPUT<br>$\mu$ Eq/kg/<br>15min  |      |                 |                | SAL *           | 9.8 $\pm$ 0.75  |
|                                                    | NB   | 10.2 $\pm$ 2.06 | 6.4 $\pm$ 1.17 | HIST            | 19.5 $\pm$ 1.27 |
|                                                    |      |                 | +              | PG              | 19.5 $\pm$ 1.31 |
| K <sup>+</sup><br>OUTPUT<br>$\mu$ Eq/kg/<br>15min) |      |                 |                | SAL *           | 4.7 $\pm$ 1.06  |
|                                                    | B♦   | 5.9 $\pm$ 1.49  | 2.6 $\pm$ 0.51 | HIST            | 16.4 $\pm$ 1.72 |
|                                                    |      |                 | +              | PG              | 15.7 $\pm$ 1.91 |

- \* Response to this infusion significantly different ( $p<0.05$ ) from responses to other infusions  
 ♦ B significantly different ( $p<0.05$ ) from NB  
 + Pyrilamine significantly different ( $p<0.05$ ) from other time blocks

Potassium ion output. (Table 11) Compared to pre-infusion, the output of potassium increased significantly ( $p=0.0001$ ) after infusion was begun. While, the actual

output stimulated by the infusion of pentagastrin and histamine did not differ significantly, both were significantly greater ( $p < 0.00001$ ) than that during saline infusion. Also,  $K^+$  output was significantly greater ( $p < 0.00001$ ) in experiments with no balloon than those with a balloon obstructing the pylorus, irrespective of infusion composition.

Chloride ion concentration. (Table 12) The chloride ion concentration was relatively constant among all experiments. The only significant difference was balloon experiment results were higher ( $p = 0.00035$ ) than when there was no balloon.

Chloride ion output. (Table 12) Because of minimal changes in  $[Cl^-]$ , the chloride output related closely to changes in volume. The output of chloride ion increased significantly ( $p = 0.0001$ ) throughout the infusion period and the drug\*time interaction was significant ( $p = 0.0001$ ), since pentagastrin rapidly induced a marked increase, that was significantly greater than that of histamine ( $p = 0.0495$ ) or saline ( $p = 0.0001$ ). Histamine also produced an increased output over time that was significantly greater than that of saline ( $p = 0.0013$ ). The drug\*balloon interaction was

significant ( $p=0.04872$ ). In SAL/NB experiments, the output of chloride ion was significantly less than either HIST/NB ( $p=0.00059$ ) or PG/NB ( $p<0.00001$ ), and during PG/NB, output was significantly greater than during HIST/NB ( $p=0.00001$ ).

Table 12.  
CHLORIDE IN GASTRIC CONTENTS  
Mean  $\pm$  SEM

|                                                    | B/NB           | BASAL            | PYRILAMINE       | INFUSIONS (max) |                   |
|----------------------------------------------------|----------------|------------------|------------------|-----------------|-------------------|
| [Cl <sup>-</sup> ]<br>mEq/L                        |                |                  |                  | SAL             | 143.2 $\pm$ 3.82  |
|                                                    | NB             | 143.4 $\pm$ 5.6  | 143.1 $\pm$ 6.32 | HIST            | 144.9 $\pm$ 3.62  |
|                                                    |                |                  |                  | PG              | 144.0 $\pm$ 6.68  |
| [Cl <sup>-</sup> ]<br>mEq/L                        |                |                  |                  | SAL             | 151.3 $\pm$ 5.07  |
|                                                    | B $\spadesuit$ | 151.1 $\pm$ 5.2  | 153.3 $\pm$ 5.57 | HIST            | 156.9 $\pm$ 3.53  |
|                                                    |                |                  |                  | PG              | 154.0 $\pm$ 2.56  |
| CL <sup>-</sup><br>OUTPUT<br>$\mu$ Eq/kg/<br>15min |                |                  |                  | SAL *           | 143.3 $\pm$ 8.82  |
|                                                    | NB             | 138.8 $\pm$ 22.7 | 111.1 $\pm$ 17.8 | HIST*           | 207.3 $\pm$ 20.45 |
|                                                    |                |                  | +                | PG *            | 272.9 $\pm$ 19.47 |
| CL <sup>-</sup><br>OUTPUT<br>$\mu$ Eq/kg/<br>15min |                |                  |                  | SAL *           | 73.7 $\pm$ 14.07  |
|                                                    | B $\spadesuit$ | 82.2 $\pm$ 16.93 | 51.0 $\pm$ 10.44 | HIST*           | 149.2 $\pm$ 19.53 |
|                                                    |                |                  | +                | PG *            | 172.0 $\pm$ 19.07 |

\* Response to this infusion significantly different ( $p<0.05$ ) from responses to other infusions

$\spadesuit$  B significantly different ( $p<0.05$ ) from NB

+ Pyrilamine significantly different ( $p<0.05$ ) from other time

In the balloon experiments, pentagastrin stimulated outputs that were significantly greater than histamine ( $p=0.04704$ )

and saline ( $p < 0.00001$ ) and histamine stimulated outputs that were significantly greater than saline ( $p = 0.00024$ ). Overall, the balloon experiments resulted in significantly less chloride output ( $p < 0.00001$ ) than the no balloon experiments. The drug effect on chloride output was significant ( $p < 0.00001$ ) and all three infusions differed significantly.

Hydrogen ion (acid) concentration. (Table 13) As infusions were begun, the acid concentration increased significantly ( $p = 0.0001$ ) over time. The different infusions responded significantly differently ( $p = 0.0001$ ) over time. Saline slowly increased from the "R2" period, while pentagastrin ( $p = 0.0341$ ) and histamine ( $p = 0.0001$ ) increased significantly more rapidly. The histamine response was also significantly ( $p = 0.0023$ ) more profound than that of pentagastrin. The difference between those experiments with the balloon and those without balloon was also significant ( $p < 0.00001$ ). In addition, the  $[H^+]$  in PG/NB was significantly less ( $p < 0.00005$ ) for all time points than PG/B. During the last three collections, HIST/B had a significantly greater ( $p < 0.03$ )  $[H^+]$  than HIST/NB.

The overall drug effect on  $[H^+]$  was significant ( $p < 0.00001$ ) and there were significant differences between

each of the infusions, as well. Histamine infusion produced  $[H^+]$  significantly greater than pentagastrin ( $p=0.00002$ ) or saline ( $p<0.00001$ ), and pentagastrin infusion was significantly greater than saline ( $p=0.00003$ ). There was a significant ( $p=0.00327$ ) drug\*balloon interaction. The  $[H^+]$  during HIST/NB was significantly greater than SAL/NB ( $p<0.00001$ ) or PG/NB ( $p<0.00001$ ), while there was no significant difference in  $[H^+]$  between SAL/NB and PG/NB. In the balloon experiment, there was no significant difference in  $[H^+]$  for HIST/B and PG/B; however SAL/B produced an  $[H^+]$  significantly less ( $p<0.00001$ ) than either HIST/B or PG/B.

Acid output. (Table 13) Acid output was significantly ( $p=0.0001$ ) affected by time and by drug\*time interaction. The output increased following the initiation of infusion. The pattern of increasing acid output was not significantly different between histamine and pentagastrin infusions, though each led to significantly greater ( $p=0.0001$ ) output changes than during saline infusion. All three infusions resulted in significantly different ( $p<0.00001$ ) acid outputs. Histamine-induced outputs were significantly greater than those of pentagastrin ( $p=0.00120$ ), and outputs

under both histamine and pentagastrin were significantly greater ( $p < 0.00001$ ) than that of saline.

Table 13.  
ACID IN THE GASTRIC CONTENTS  
Mean  $\pm$  SEM

|                                                | B/NB | BASAL            | PYRILAMINE       | INFUSIONS (max) |                   |
|------------------------------------------------|------|------------------|------------------|-----------------|-------------------|
| [H <sup>+</sup> ]<br>mEq/L                     |      |                  |                  | SAL *           | 28.9 $\pm$ 5.47   |
|                                                | NB   | 33.8 $\pm$ 6.53  | 27.6 $\pm$ 6.59  | HIST§           | 80.3 $\pm$ 4.86   |
|                                                |      |                  | +                | PG              | 42.4 $\pm$ 3.14   |
| [H <sup>+</sup> ]<br>mEq/L                     |      |                  |                  | SAL *           | 38.75 $\pm$ 9.09  |
|                                                | B♦   | 47.0 $\pm$ 10.15 | 32.81 $\pm$ 9.32 | HIST            | 103.12 $\pm$ 3.48 |
|                                                |      |                  | +                | PG              | 84.17 $\pm$ 4.94  |
| H <sup>+</sup> OUTPUT<br>$\mu$ Eq/kg/<br>15min |      |                  |                  | SAL *           | 28.6 $\pm$ 5.51   |
|                                                | NB   | 35.5 $\pm$ 10.23 | 22.5 $\pm$ 7.43  | HIST§           | 112.6 $\pm$ 8.31  |
|                                                |      |                  | +                | PG              | 80.2 $\pm$ 6.99   |
| H <sup>+</sup> OUTPUT<br>$\mu$ Eq/kg/<br>15min |      |                  |                  | SAL *           | 21.78 $\pm$ 6.99  |
|                                                | B♦   | 29.52 $\pm$ 9.53 | 12.78 $\pm$ 5.14 | HIST            | 97.03 $\pm$ 10.82 |
|                                                |      |                  | +                | PG              | 91.22 $\pm$ 5.85  |

+ Pyrilamine significantly less ( $p < 0.05$ ) than other time blocks

♦ B significantly different ( $p < 0.05$ ) from NB

§ Histamine significantly different ( $p < 0.05$ ) than other infusions

\* Response to this infusion significantly different ( $p < 0.05$ ) from responses to other infusions

Acid output was also significantly affected ( $p = 0.00054$ ) by the drug\*balloon interaction. In the no balloon experiments, all three infusions resulted in different outputs of acid. HIST/NB resulted in outputs significantly

greater ( $p < 0.00001$ ) than both PG/NB and SAL/NB. PG/NB outputs were also significantly greater ( $p = 0.00001$ ) than SAL/NB. The addition of the balloon dramatically changed the output differences, since HIST/B was not significantly different than PG/B. However, both PG/B and HIST/B produced outputs significantly greater ( $p < 0.00001$ ) than SAL/B.

Sodium ion concentration. (Table 14) The concentration of sodium decreased significantly ( $p = 0.0001$ ) over the time course of infusion. A significant ( $p = 0.0001$ ) drug\*time interaction was observed. Specifically, the decrease following histamine infusion was significantly more dramatic than with pentagastrin ( $p = 0.0002$ ) or saline ( $p = 0.0001$ ). Pentagastrin and saline did not differ significantly.

The effect of the balloon on  $[Na^+]$  was also significant ( $p = 0.00002$ ), and under balloon conditions the  $[Na^+]$  differed significantly ( $p < 0.00001$ ) in response to each of the infusion compositions. Sodium concentration was significantly less during histamine infusion than either pentagastrin ( $p = 0.00001$ ) or saline ( $p < 0.00001$ ), and was significantly less ( $p = 0.00020$ ) during pentagastrin infusion than during saline infusion. At all time points, the PG/B

experiments yielded a  $[Na^+]$  that was significantly less ( $p < 0.01$ ) than during the PG/NB experiments.

Table 14.  
SODIUM IN GASTRIC CONTENTS  
Mean  $\pm$  SEM

|                                                     | B/NB | BASAL            | PYRILAMINE       | INFUSIONS (max) |                   |
|-----------------------------------------------------|------|------------------|------------------|-----------------|-------------------|
| $[Na^+]$<br>mEq/L                                   |      |                  |                  | SAL *           | 108.0 $\pm$ 4.64  |
|                                                     | NB   | 101.5 $\pm$ 8.15 | 107.0 $\pm$ 6.08 | HIST§           | 52.5 $\pm$ 5.22   |
|                                                     |      |                  | +                | PG              | 88.2 $\pm$ 4.78   |
| $[Na^+]$<br>mEq/L                                   |      |                  |                  | SAL *           | 91.56 $\pm$ 9.54  |
|                                                     | B    | 89.63 $\pm$ 9.17 | 102.04 $\pm$ 9.1 | HIST§           | 31.10 $\pm$ 4.15  |
|                                                     |      |                  | +                | PG              | 57.73 $\pm$ 6.08  |
| Na <sup>+</sup><br>OUTPUT<br>$\mu$ Eq/kg/<br>15min  |      |                  |                  | SAL *           | 108.8 $\pm$ 8.80  |
|                                                     | NB   | 99.2 $\pm$ 12.27 | 82.2 $\pm$ 12.03 | HIST§           | 77.1 $\pm$ 12.91  |
|                                                     |      |                  | +                | PG              | 167.4 $\pm$ 14.69 |
| Na <sup>+</sup><br>OUTPUT<br>$\mu$ Eq/kg/<br>15min) |      |                  |                  | SAL             | 44.87 $\pm$ 7.07  |
|                                                     | B†   | 45.81 $\pm$ 7.44 | 32.52 $\pm$ 4.98 | HIST            | 30.10 $\pm$ 6.60  |
|                                                     |      |                  | +                | PG ‡            | 68.62 $\pm$ 16.24 |

- + Pyrilamine significantly less ( $p < 0.05$ ) than other time blocks
- ♦ B significantly different ( $p < 0.05$ ) from NB
- \* Response to this infusion significantly different ( $p < 0.05$ ) from responses to other infusions
- § Histamine significantly different ( $p < 0.05$ ) than other infusions
- † Pentagastrin significantly different ( $p < 0.05$ ) than histamine

Sodium output. (Table 14) Time ( $p = 0.0488$ ),

balloon\*time interaction ( $p = 0.0105$ ), drug\*time interaction ( $p = 0.0008$ ), balloon ( $p < 0.00001$ ), drug ( $p < 0.00001$ ), and

drug\*balloon interaction ( $p=0.00023$ ) are all significant for sodium output. Over time, histamine and saline resulted in relatively constant sodium outputs, whereas, pentagastrin resulted significantly different ( $p=0.0001$ , and  $0.0277$ , respectively) fluctuations in sodium output. Sodium output during pentagastrin infusion was significantly greater than during histamine ( $p<0.00001$ ) and saline ( $0.00003$ ) infusion. It was also significantly greater ( $p=0.00137$ ) during saline than histamine infusion. The output during PG/NB was significantly greater ( $p<0.00001$ ) than either HIST/NB or SAL/NB, while SAL/NB was significantly greater ( $p=0.00141$ ) than HIST/NB. Sodium output during SAL/B was not significantly different than either PG/B or HIST/B; however, output during HIST/B was significantly less ( $p=0.01197$ ) than PG/B. Most importantly, throughout the infusions, the output during PG/NB was significantly greater ( $p<0.00001$ ) than PG/B, HIST/NB was significantly greater ( $p<0.003$ ) than HIST/B, and SAL/NB was significantly greater ( $p<0.0002$ ) than SAL/B.

### Pre-infusion

### Duodenal samples

(See Tables 15,16,17,18,19)

The presence or absence of the pyloric obstruction did not change the appearance of the fluid collected from the duodenal catheter. Duodenal samples were transparent dark yellow to dark green colored and generally thick and mucoid. The volume collected was related to viscosity of samples and limited by the small diameter of the catheter; therefore, outputs of electrolytes were not calculated. Duodenal fluid was observed to be less viscid, however, during times in which a high volume was collected. No fluid was obtained from the duodenal catheter during 19 (11 pre infusion; 8 post infusion: 16 without obstruction; 3 with obstruction) of the 432 samples collected. The only significant difference was in balloon status for volume and bicarbonate ion concentration. The volume from the duodenal catheter was significantly ( $p < 0.00001$ ) greater in experiments with the balloon obstructing the pylorus. Bicarbonate ion concentration was also significantly ( $p = 0.00353$ ) greater in experiments with pyloric obstruction. As with gastric samples, "basal" and "pyrilamine" values were derived from

"R1" and "R2" since there were no significant differences between results of each infusion during this pre-infusion time.

### Post-infusion

### Duodenal samples

Bicarbonate ion concentration. (Table 15) The concentration of bicarbonate ion was significantly greater ( $p=0.00397$ ) in collections made while the balloon was in place. There was also a significant ( $p=0.00002$ ) drug effect on  $[\text{HCO}_3^-]$ . Pentagastrin infusion resulted in  $[\text{HCO}_3^-]$

Table 15.  
BICARBONATE IN DUODENAL CONTENTS  
Mean  $\pm$  SEM

|                             | B/NB | BASAL          | PYRILAMINE     | INFUSIONS |                |
|-----------------------------|------|----------------|----------------|-----------|----------------|
| $[\text{HCO}_3^-]$<br>mEq/L |      |                |                | SAL       | 23.6 $\pm$ 2.7 |
|                             | NB   | 23.2 $\pm$ 2.6 | 16.2 $\pm$ 1.5 | HIST      | 22.9 $\pm$ 2.3 |
|                             |      |                |                | PG *      | 33.0 $\pm$ 2.3 |
| $[\text{HCO}_3^-]$<br>mEq/L |      |                |                | SAL       | 28.5 $\pm$ 4.7 |
|                             | B ♦  | 28.5 $\pm$ 2.7 | 28.7 $\pm$ 2.7 | HIST      | 28.3 $\pm$ 1.9 |
|                             |      |                |                | PG *      | 37.1 $\pm$ 2.1 |

\* Response to this infusion significantly different ( $p<0.05$ ) from responses to other infusions

♦ B significantly different ( $p<0.05$ ) from NB

significantly greater than histamine ( $p=0.00016$ ) and saline ( $p=0.00001$ ). The  $[\text{HCO}_3^-]$  did not differ significantly between histamine and saline.

Sodium ion concentration. (Table 16) The only significant effect observed for  $[\text{Na}^+]$  in duodenal collection was a drug effect ( $p=0.0467$ ). During histamine infusion, the fluid collected had a significantly lower  $[\text{Na}^+]$  than during pentagastrin ( $p=0.04231$ ) or saline ( $p=0.02316$ ) infusion.

Table 16.  
SODIUM IN DUODENAL CONTENTS  
Mean  $\pm$  SEM

|                          | B/NB | BASAL           | PYRILAMINE      | INFUSIONS |                 |
|--------------------------|------|-----------------|-----------------|-----------|-----------------|
| $[\text{Na}^+]$<br>mEq/L |      |                 |                 | SAL       | 149.0 $\pm$ 5.6 |
|                          | NB   | 147.5 $\pm$ 3.9 | 151.5 $\pm$ 6.7 | HIST *    | 135.0 $\pm$ 3.0 |
|                          |      |                 |                 | PG        | 144.9 $\pm$ 2.4 |
| $[\text{Na}^+]$<br>mEq/L |      |                 |                 | SAL       | 147.8 $\pm$ 5.5 |
|                          | B    | 143.1 $\pm$ 5.5 | 142.9 $\pm$ 6.1 | HIST *    | 143.1 $\pm$ 2.2 |
|                          |      |                 |                 | PG        | 152.6 $\pm$ 5.2 |

\* Response to this infusion significantly different ( $p<0.05$ ) from responses to other infusions

Potassium ion concentration. (Table 17) Over the 90 minutes of infusion, there was a significant ( $p=0.0019$ ) time effect of decreasing  $[\text{K}^+]$ . The drug effect was also significant ( $p=0.00906$ ), with concentrations after starting

infusions of histamine ( $p=0.00783$ ) or pentagastrin ( $p=0.00653$ ) decreasing significantly compared to saline.

Table 17.  
POTASSIUM IN DUODENAL CONTENTS  
Mean  $\pm$  SEM

|                            | B/NB | BASAL         | PYRILAMINE    | INFUSIONS |                 |
|----------------------------|------|---------------|---------------|-----------|-----------------|
| [K <sup>+</sup> ]<br>mEq/L |      |               |               | SAL *     | 4.26 $\pm$ 0.27 |
|                            | NB   | 4.5 $\pm$ 0.2 | 4.4 $\pm$ 0.3 | HIST      | 3.90 $\pm$ 0.20 |
|                            |      |               |               | PG        | 3.64 $\pm$ 0.10 |
| [K <sup>+</sup> ]<br>mEq/L |      |               |               | SAL *     | 3.94 $\pm$ 0.14 |
|                            | B    | 4.1 $\pm$ 0.2 | 4.0 $\pm$ 0.2 | HIST      | 3.69 $\pm$ 0.12 |
|                            |      |               |               | PG        | 3.74 $\pm$ 0.27 |

\* Response to this infusion significantly different ( $p<0.05$ ) from responses to other infusions

Table 18.  
CHLORIDE IN DUODENAL CONTENTS  
Mean  $\pm$  SEM

|                             | B/NB | BASAL           | PYRILAMINE      | INFUSIONS |                 |
|-----------------------------|------|-----------------|-----------------|-----------|-----------------|
| [Cl <sup>-</sup> ]<br>mEq/L |      |                 |                 | SAL *     | 135.6 $\pm$ 5.5 |
|                             | NB   | 118.1 $\pm$ 5.5 | 119.6 $\pm$ 5.2 | HIST      | 103.3 $\pm$ 7.0 |
|                             |      |                 |                 | PG        | 115.1 $\pm$ 6.1 |
| [Cl <sup>-</sup> ]<br>mEq/L |      |                 |                 | SAL *     | 129.2 $\pm$ 6.3 |
|                             | B    | 126.6 $\pm$ 7.1 | 123.9 $\pm$ 4.4 | HIST      | 112.5 $\pm$ 2.7 |
|                             |      |                 |                 | PG        | 108.5 $\pm$ 2.7 |

\* Response to this infusion significantly different ( $p<0.05$ ) from responses to other infusions

Chloride ion concentration. (Table 18) The drug effect on [Cl<sup>-</sup>] was significant ( $p<0.00001$ ). The [Cl<sup>-</sup>] was

significantly greater ( $p=0.00001$ ) during saline infusion than during either histamine or pentagastrin infusion.

Volume. (Table 19) The volume of fluid collected from the duodenal catheter increased significantly ( $p=0.0378$ ) compared to pre-infusion during the first 30 minutes after the infusions started and then gradually decreased throughout the remaining 60 minutes of infusion to volumes slightly greater than basal. The presence of pyloric obstruction by the balloon significantly ( $p<0.00001$ ) increased the volume collected. The infusion composition resulted in significant differences ( $p=0.00005$ ), with pentagastrin yielding volumes significantly greater than either histamine ( $p=0.00008$ ) or saline ( $p=0.00009$ ), while histamine and saline did not differ significantly from each other. In the experiments without the balloon, there was no significant difference between infusion volume; however, with balloon, pentagastrin-induced volumes were significantly greater than during either histamine ( $p<0.00001$ ) or saline ( $p<0.00001$ ) infusion.

Table 19.  
VOLUME OF DUODENAL CONTENTS  
Mean  $\pm$  SEM

|                    | B/NB | BASAL            | PYRILAMINE       | INFUSIONS |                  |
|--------------------|------|------------------|------------------|-----------|------------------|
| VOLUME<br>ml/15min |      |                  |                  | SAL       | 75.0 $\pm$ 24.8  |
|                    | NB   | 64.3 $\pm$ 25.9  | 64.5 $\pm$ 18.3  | HIST      | 58.9 $\pm$ 24.8  |
|                    |      |                  |                  | PG        | 64.5 $\pm$ 15.7  |
| VOLUME<br>ml/15min |      |                  |                  | SAL       | 181.0 $\pm$ 49.8 |
|                    | B♦   | 217.2 $\pm$ 49.5 | 214.6 $\pm$ 45.0 | HIST      | 155.6 $\pm$ 16.4 |
|                    |      |                  |                  | PG*       | 409 $\pm$ 111.5  |

\* Significantly different ( $p < 0.05$ ) from other infusions

♦ B significantly different ( $p < 0.05$ ) from NB

### Bile Acids

Bile acid concentration was measured in a selected number of the 45 minute collection. The lower limit of the Enzabile test was 5  $\mu\text{mol/L}$ . Bile acid concentrations during the balloon experiments were significantly less than no balloon experiments ( $p = 0.000981$ ). In the occlusion studies, the bile acid concentration was  $< 5 \mu\text{mol/L}$  in 12 of 18 trials. The remaining balloon trials had concentrations of 5  $\mu\text{mol/L}$  in 4 trials, 6  $\mu\text{mol/L}$  in 1 trial, and 7  $\mu\text{mol/L}$  in 1 trial. The concentration ranged from 21 to 77  $\mu\text{mol/L}$  in the NB studies, with a mean of 42  $\mu\text{mol/L}$ .

### Discussion

The placement of a duodenal catheter through the indwelling gastric cannula has been used to analyze duodenal contents and has been shown to allow simultaneous collection of gastric and duodenal contents during both resting and stimulated conditions. (See Chap. 4) This technique was further modified in this study to provide a method to occlude the pylorus to collect gastric contents that were devoid of reflux from the duodenum. The previous studies with the catheter suggest the reflux of duodenal fluid which has been shown during endoscopic examination to occur spontaneously in fasted animals<sup>50,51</sup> may be enhanced by the presence of the catheter passing through the pylorus. (See Chap. 4) The absence of bile acids in the gastric contents during the balloon experiments confirmed that reflux of duodenal contents was eliminated. This technique allowed us, therefore, to collect purely gastric or duodenal contents during the balloon experiments, whereas, in the no balloon experiments, the gastric contents were comparable to

those of previous equine secretory studies without any kind of catheter in place.

The pretreatment of the horses with pyrilamine maleate in all experiments was necessary to allow for comparison of histamine and pentagastrin. The results of the pyrilamine pretreatment were not significantly different between groups, however, they were significantly different from basal collections prior to treatment. These results are consistent with previous findings suggesting that the equine acid secretory response may be dampened by the administration of an H-1 receptor antagonist. (See Chap. 3) In this study, as predicted, collection volume, acid concentration, and acid, sodium, potassium and chloride outputs decreased following infusion of pyrilamine maleate, while the pH and sodium concentration of the gastric contents increased.

The trends observed during the NB experiments were consistent with the species specific equine response that has been observed in earlier studies as distinct from the results observed in other species during similar stimulation.<sup>31,44</sup> The infusion of both pentagastrin and histamine resulted in the stimulation of increased acid

output.<sup>31,44</sup> (See Chap. 2) Nevertheless, the peak acid concentrations were significantly higher with histamine stimulation than with pentagastrin stimulation, and sodium output increased during pentagastrin stimulation and decreased slightly during histamine stimulation.

In the preinfusion time blocks, the volume of gastric collections were significantly less in the B than the NB experiments, suggesting that an extragastric source of fluid might be contributing to the volume collected from the gastric cannula in horses. The fluid collected in the B experiments also had a higher concentration of HCl than that of the NB experiments, which added credence to the dilution theory. Since the  $[Na^+]$  and  $[K^+]$  did not differ between B and NB experiments, this extragastric fluid apparently contains these ions. Duodenal fluid has a high concentration of sodium, a slightly lower concentration of potassium and chloride, and an approximately isotonic concentration of bicarbonate compared to gastric fluid. (See Chap. 4) The introduction of duodenal fluid into the gastric collection may be enhanced by the presence of the catheter in the NB experiments, but its reflux into the

stomach appears to be a consistent feature of equine upper GI function, even without transpyloric catheterization.

During infusions, the volume continued to be significantly greater in the NB experiments than the B experiments. Pentagastrin experiments resulted in greater volumes than histamine experiments, which in turn had greater volumes than the saline experiments. The differences were markedly greater in the NB experiments than the B experiments. These findings were consistent, irregardless of balloon status. Therefore, pentagastrin infusion appears to stimulate a larger fluid response than does histamine, while both result in equivalent maximal acid outputs. A portion of this fluid is of gastric origin, since pyloric obstruction does not eliminate the volume differences. The absolute volume differences between PG/B and HIST/B were not large as those between either of these and SAL/B, however, the difference was significant. The suggestion is that a nonparietal component of gastric secretion may be responsive to stimulation by pentagastrin. It is also possible that this discrepancy results from unnoticed leakage around the balloon, since in preliminary trials with this system, we discovered that additional air

had to be injected into the balloon during initiation of pentagastrin infusion to prevent visible leakage of yellow duodenal contents. Gastrin receptors have been identified on smooth muscle cells in the gastric antrum in dogs and gastrin has been shown to relax the pylorus to enhance gastric emptying.<sup>95,96</sup> Pentagastrin may stimulate these smooth muscle receptors in the horse and allow additional reflux of duodenal contents.

As expected, and in accordance with previous studies, potassium concentration and output increased in parallel with an increasing acid concentration and output during stimulation.<sup>44</sup> However, the output of potassium was significantly greater in the NB experiments, suggesting that it is one of the components of the extragastric fluid which is separated out by the occlusion of the pylorus.

Whereas, the lower  $[Cl^-]$  in the NB experiments was likely secondary to the dilutional effect of the extragastric portion of these collections, chloride output was greater in the NB experiments, inferring that the extragastric fluid contains chloride, but at a lesser concentration than that of gastric secretions. Significantly greater chloride output during pentagastrin infusion in both NB and B experiments in contrast to the

histamine response, further implies a special pentagastrin effect.

The finding that during the NB experiments the maximal acid concentration induced by histamine was significantly greater than that induced by pentagastrin, whereas, in the B experiments, maximal histamine and pentagastrin related acid concentrations were equivalent suggests that the equine stomach *per se*, responds to these 2 secretagogues in a

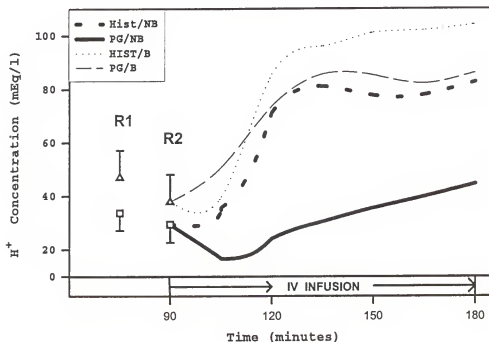


Figure 8 Acid concentration. A curvilinear line derived from mean sodium output during pentagastrin and histamine infusions comparison of B and NB experiments.  $\Delta$  marks mean for B trials  $\square$  marks mean for NB trials.

manner similar to that seen in other monogastric species. (See fig. 8) In some of the HIST/NB experiments, the acid concentration was less than corresponding HIST/B experiments, this is probably related to dilution by some extragastric fluid that is responsible for a portion of the increased volume of collection, but not to the same magnitude stimulated by pentagastrin.

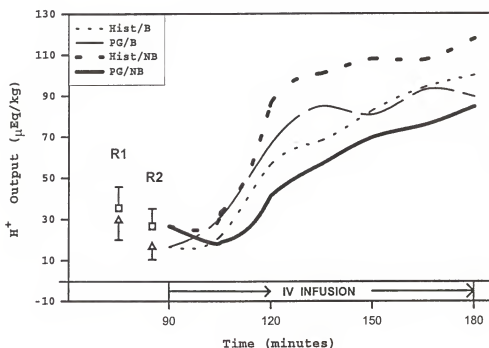


Figure 9 Acid output. A curvilinear line derived from mean sodium output during pentagastrin and histamine infusions comparison of B and NB experiments.  $\Delta$  marks mean for B trials  $\square$  marks mean for NB trials.

Acid output in the B experiments was equal during pentagastrin and histamine stimulation, however, in the NB experiments, histamine related acid output was greater than that of pentagastrin. (See fig. 9) Several factors seem to be involved in this unexpected finding. The HIST/NB maximal acid output was greater than HIST/B during some of the time blocks, while the opposite relationship was noted for PG/B and PG/NB. The lower maximal acid output in the PG/NB may be the result of the loss of hydrogen ions through chemical reaction with bicarbonate ions from the extragastric component of NB collections.

Even more dramatic than the effects on acid were those on sodium recorded in these experiments. (See fig. 10) As with acid concentration, the pattern of the  $[Na^+]$  response to PG/B was that expected of the classic parietal secretory response rather than the profound nonparietal response seen in previous equine pentagastrin studies. The comparison of sodium outputs under B vs. NB conditions was still more spectacular. (See fig. 11) Sodium output was greater in all NB experiments than those with the balloon, which is consistent with the suggestion that the extragastric

presumably duodenal, fluid that accounts for the additional volume is sodium rich.

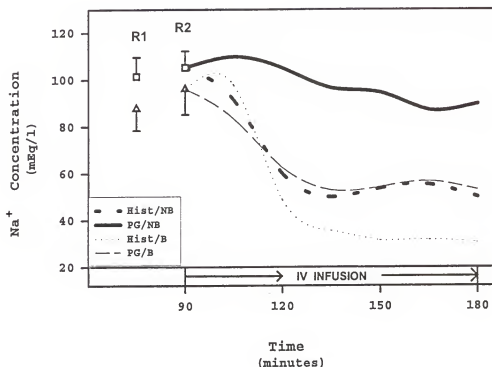


Figure 10 Sodium concentration. A curvilinear line derived from mean sodium output during pentagastrin and histamine infusions comparison of B and NB experiments.  $\Delta$  marks mean for B trials  $\square$  marks mean for NB trials.

The duodenal contents sampled by the intraduodenal catheter are presumably composed of a combination of biliary, duodenal, and pancreatic secretions. Not surprisingly, the volume of collection was much greater in the experiments with pyloric obstruction, which likely

resulted in the accumulation of these secretions in the proximal duodenum. The significantly greater volumes observed during pentagastrin infusions were of particular

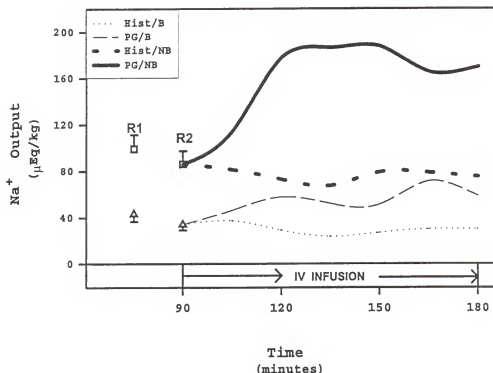


Figure 11 Sodium output. A curvilinear line derived from mean sodium output during pentagastrin and histamine infusions comparison of B and NB experiments.  $\Delta$  marks mean for B trials  $\square$  marks mean for NB trials.

interest. Furthermore, the fluid collected during these experiments appeared to be less viscous than in experiments with either histamine or saline infusion. The duodenal contents collected during pentagastrin infusion also had a

higher concentration of bicarbonate. These findings are consistent with a report by Alexander and Hickson that pentagastrin is a strong stimulant of equine pancreatic secretion.<sup>55</sup>

The suggestion that the equine gastric contents might contain fluid originating from the duodenum is not new or without warrant.<sup>50,51</sup> Anatomically, the position of the proximal duodenum in relation to the stomach allows gravity to aid in this reflux. In addition, the bile and pancreatic ducts of horses enter the duodenum relatively near to the pyloric sphincter, and reflux of duodenal contents into the gastric lumen has been seen during endoscopic examination.<sup>50,51</sup> In man, duodenogastric reflux has been recognized and is quantified by the measurement of sodium ions in gastric contents.<sup>92,93</sup>

Pancreatic secretion in the horse is reported to be continuous and profuse with a higher concentration of chloride and lower concentration of bicarbonate than that of other monogastric species.<sup>55-57</sup> The fivefold increase in pancreatic secretion after the administration of pentagastrin appears to be unique to the horse, among the species that have been studied.<sup>55</sup> In most species,

pancreatic fluid and electrolyte secretion is regulated primarily by secretin with some modulation via vagal reflexes, whereas enzyme secretion is primarily controlled by CCK and vagal input.<sup>59,60</sup> Secretin induces pancreatic duct cells to produce increased volumes of fluid and as the secretory rate increases, there is a reciprocal switch in the bicarbonate and chloride concentrations.<sup>63</sup> In the horse, the concentration of bicarbonate is never greater than that of chloride, even during maximal secretion.<sup>55</sup> Enzyme content of pancreatic secretions increase with the stimulation of CCK-A receptors on the pancreatic acinar cells in most species.<sup>60,61</sup> The concentration of enzymes in equine pancreatic secretion is very low under both basal and stimulated conditions.<sup>55</sup> Gastrin, which acts at CCK-B receptors, is a weak stimulant of pancreatic enzyme and fluid secretion in species other than the horse.<sup>62</sup> The relative prevalence of CCK-A and CCK-B receptors within the equine gastrointestinal tract has not been reported. The results of this study and the report of Alexander and Hickson might mean that the equine pancreas, and in particular pancreatic duct cells, has an abundance of CCK-B receptors.

Biliary secretion has an electrolyte composition similar to that of the pancreas, and ductular secretion is stimulated by secretin with a corresponding increased bicarbonate concentration.<sup>97</sup> Gastrin, but not pentagastrin, has been shown to increase biliary flow in dogs.<sup>97</sup> The horse lacks a gallbladder and is reported to have continuous biliary flow<sup>55</sup>, though which substances are involved in the regulation of this flow, has not been reported. Increased biliary secretion in response to pentagastrin is also a possible source of some of the extragastric fluid in equine gastric collections.

This study clearly demonstrates that pentagastrin stimulates the secretion of an extragastric fluid which dilutes the gastric contents during gastric collection from the gastric cannula model. With separation of gastric and extragastric secretions by obstruction of the pylorus, it becomes apparent that pentagastrin does stimulate parietal secretion comparable to that of histamine, similarly comparable to that of other monogastric species. Although, the exact origin of this extragastric fluid requires further investigation, it is most likely of pancreatic and/or biliary origin. The remarkable volume response to

pentagastrin when collecting gastric contents from the horse via the cannula is related primarily to increased duodenogastric reflux of sodium rich isotonic fluid. Histamine infusion, on the other hand, stimulates the parietal cells, but does not stimulate the secretion of the extragastric secretion. Thus, the equine specific gastric secretory response to pentagastrin is the result of extragastric actions of pentagastrin rather than species variation in the acid secretory response.

## CHAPTER 6

### SUMMARY AND CONCLUSIONS

#### Summary

Histamine infusion at a dose of 30  $\mu\text{g/kg-hr}$  to horses resulted in a maximal acid output response comparable to the maximal response to pentagastrin infusion and, on a bodyweight basis is similar to that of humans. Thus, the gastric contents collected during histamine infusion differed significantly in electrolyte concentrations and sodium output from those collected during pentagastrin infusion. The character of the histamine-stimulated gastric contents resembles the classic "parietal" response described in other species and did not include the voluminous sodium-rich component described in studies with pentagastrin.<sup>31,44,49,51,53,54</sup>

Prior to this study, we had some concerns about the reaction of horses to the histamine infusion. In the pilot

study, no adverse reactions were observed during the histamine infusions; however, some horses became anxious during and for approximately 15 minutes after the pyrilamine maleate administration. The second histamine dose-response study was designed with a slower infusion of pyrilamine, which eliminated the excitement problem. It is the results of this second histamine study that are presented in Chapter 2. The study was designed with 4 doses of histamine, yet only 3 doses were statistically analyzed. We were able to complete the all 4 doses in only one horse, due to metabolic complications in the other horses associated with the loss of large amounts of HCl, not a direct histamine effect. Histamine infusion with associated gastric collection done in later studies (See Chap. 5) was free of such complications.

Pretreatment with pyrilamine maleate or another H-1 receptor antagonist was necessary to prevent CNS and respiratory complication during histamine infusion.<sup>65</sup> In these studies, it was observed that acid output decreased after pyrilamine, in contrast to what is seen in other species.<sup>29,71,77,82,83</sup> In preparation for later studies comparing histamine to pentagastrin, we decided to

investigate the effect of pyrilamine maleate pretreatment on pentagastrin stimulated gastric contents. Chapter 3 presents the surprising results of this study. Acid output after pyrilamine maleate was significantly decreased from basal, and the secretory response to pentagastrin stimulation was also diminished.

The primary goal of this project was to determine whether the large sodium-rich component of gastrin contents in response to pentagastrin stimulation was of gastric or extragastric origin. After attempts to surgically isolate the stomach from the proximal duodenum failed, a technique was developed to obstruct the pylorus temporarily. This involved the passage of an endoscope through the gastric cannula into the stomach and then guiding it into the proximal duodenum. The process of passing the endoscope into the duodenum, introducing the stylet through the biopsy channel, removing the endoscope with the stylet still in place and then threading the specially designed catheter over the stylet took 15 to 30 minutes.

Because the duodenal catheterization involved manipulation within the gastric lumen and resulted in an object traversing the pylorus throughout the entire

experiment, data were analyzed that compared the composition of contents collected from the gastric cannula with and without the catheter present. This was not a specific study, but a statistical evaluation of data collected under the two conditions. To balance the design, the "no catheter" data were those of the horses in the pyrilamine study described in Chapter 3. Chapter 4 discusses the methods and materials of the catheterization technique and the results of the comparison. The sodium output was significantly increased in the horses with an intraduodenal catheter in place and the relative electrolyte concentrations were significantly different from those where there was no catheter. The acid concentration was decreased in those experiments with the catheter present, though volume and acid output were increased.

The duodenal contents were also characterized in this chapter. Compared to the gastric contents, the fluid was found to have a higher concentration of sodium, and a lower concentration of potassium and chloride. The bicarbonate concentration was similar to plasma.

The final step in testing the hypothesis is the balloon (B) vs. no balloon (NB) study condensed into Chapter 5. The

inflation of the balloon on the intraduodenal catheter allowed obstruction of the pylorus in an attempt to prevented duodenogastric reflux. Within 15 minutes of correct positioning and adequate inflation of the balloon, it was evident that obstruction had occurred. In the no balloon experiments, the gastric contents were yellow-green and frothy in appearance. (See fig. 12) These contents had a mean bile acid concentration of 42  $\mu\text{mol/L}$ . Once the balloon



**Figure 12** Collections from catheter or cannula. KDZD is duodenal contents collected through the catheter. KDZG is gastric content collected from the cannula with the pylorus obstructed. KDUG is gastric contents collected from the cannula with no balloon on the catheter.

occluded the pylorus, the gastric contents were clear and watery, and did not contain measurable bile acids. Duodenal contents collected through the catheter with or without the balloon were thick, mucoid and yellow-green in color.

As well as changing the physical appearance of collections, obstruction of the pylorus with the balloon resulted in decreased volume and sodium and chloride output from the gastric cannula during both basal and stimulated time blocks. With the B experiments, histamine and pentagastrin infusions had comparable results, whereas, in the NB experiments, maximal pentagastrin infusion resulted in a lower acid concentration and significantly greater sodium output. That is, in the B studies, acid and sodium concentration were inversely proportional in response to both histamine and pentagastrin, and maximal acid concentration and output was equivalent.

Duodenal contents were not quantified in these experiments, as the catheter diameter was a limiting factor in the collection of this thick, often mucoid fluid. Consistently, the fluid was more profuse, less viscid and the bicarbonate concentration increased during pentagastrin

infusion. Chloride was the predominate anion even during stimulation, and sodium was the predominant cation.

### Conclusions

This series of studies build on each other to support the hypothesis of this dissertation. Reviewing the results of these studies, the following conclusions concerning the composition of equine gastric contents collected from a cannula are:

1. Histamine stimulates a purely parietal secretion, while pentagastrin induces both parietal and non-parietal secretory activity.
2. Pyrilamine maleate appears to decrease equine basal gastric acid secretion and may attenuate the acid secretory response to pentagastrin infusion.
3. The presence of a catheter passing through the pylorus into the duodenum does not prevent a normal acid secretory response to pentagastrin, but may enhance the reflux of duodenal contents into the stomach.
4. The voluminous sodium-rich fluid component of gastric contents in response to pentagastrin, is due, in large part, to duodenal reflux. The extragastric fluid refluxing into the gastric contents is most likely of pancreatic and/or biliary origin.

In addition to answering the hypothesis, these studies also led to more questions regarding equine gastric

physiology. The decreased acid output resulting from pyrilamine maleate pretreatment appears to be yet another species specific response in horses. Further investigation is necessary to determine the mechanism for this response. Although the study was able to determine that the equine-specific response to pentagastrin stimulation is of extragastric origin, still more investigation will be required to determine the exact origin of this fluid.

APPENDIX A  
HISTAMINE DOSE-RESPONSE DATA

Horses used in Histamine Study

| NAME  | BREED        | SEX | AGE  | WEIGHT |
|-------|--------------|-----|------|--------|
| Buddy | Arabian      | G   | 5 y  | 445 kg |
| Dick  | Thoroughbred | G   | 6 y  | 481 kg |
| Ethel | Thoroughbred | M   | 19 y | 493 kg |
| Harry | Thoroughbred | G   | 4 y  | 495 kg |
| Lucy  | Thoroughbred | M   | 9 y  | 506 kg |
| Tom   | Thoroughbred | G   | 4 y  | 482 kg |

HISTAMINE DOSE-RESPONSE DATA  
Volume and pH

| TIME    | DOSE     | VOLUME |     | pH    |       |
|---------|----------|--------|-----|-------|-------|
| minutes | µg/kg-hr | ml     |     |       |       |
|         |          | MEAN   | SEM | MEAN  | SEM   |
| 15      | 0        | 480    | 35  | 1.685 | 0.066 |
| 30      | 0        | 405    | 54  | 1.66  | 0.064 |
| 45      | 0        | 452    | 45  | 1.65  | 0.071 |
| 60      | HVP      | 438    | 45  | 1.597 | 0.076 |
| 75      |          | 307    | 62  | 1.707 | 0.098 |
| 90      |          | 407    | 35  | 1.872 | 0.123 |
| 105     | 7.5      | 473    | 40  | 1.695 | 0.116 |
| 120     | 7.5      | 528    | 55  | 1.502 | 0.098 |
| 135     | 7.5      | 550    | 53  | 1.468 | 0.133 |
| 150     | 7.5      | 633    | 63  | 1.445 | 0.126 |
| 165     | 15       | 598    | 69  | 1.46  | 0.137 |
| 180     | 15       | 578    | 50  | 1.423 | 0.146 |
| 195     | 15       | 605    | 41  | 1.505 | 0.205 |
| 210     | 15       | 578    | 41  | 1.452 | 0.172 |
| 225     | 30       | 600    | 48  | 1.282 | 0.039 |
| 240     | 30       | 578    | 53  | 1.266 | 0.038 |
| 255     | 30       | 466    | 90  | 1.296 | 0.059 |
| 270     | 30       | 563    | 52  | 1.29  | 0.021 |
| 285     | 45       | 470    | 130 | 1.285 | 0.005 |
| 300     | 45       | 430    | 100 | 1.42  | 0.12  |
| 315     | 45       | 455    | 35  | 1.51  | 0.24  |
| 330     | ND       | ND     | ND  | ND    | ND    |

HVP = Pyrilamine maleate infusion

ND = Not Done

HISTAMINE DOSE-RESPONSE DATA  
Acid Concentration and Output

| TIME    | DOSE     | ACID CONCENTRATION |      | ACID OUTPUT  |      |
|---------|----------|--------------------|------|--------------|------|
| minutes | µg/kg-hr | mEq/L              |      | µeq/kg-15min |      |
|         |          | MEAN               | SEM  | MEAN         | SEM  |
| 15      | 0        | 37                 | 4    | 37.3         | 6    |
| 30      | 0        | 41.1               | 5    | 36.6         | 9.4  |
| 45      | 0        | 44                 | 6.3  | 42.9         | 9.1  |
| 60      | HVP      | 42.9               | 6.7  | 39           | 8    |
| 75      |          | 38.3               | 5.1  | 26.6         | 7.1  |
| 90      |          | 28.8               | 4.3  | 25.1         | 5.7  |
| 105     | 7.5      | 47.2               | 8.8  | 47.1         | 10.2 |
| 120     | 7.5      | 65.2               | 7.1  | 73.3         | 14.3 |
| 135     | 7.5      | 71.9               | 5.5  | 82.3         | 11.5 |
| 150     | 7.5      | 72.5               | 5.95 | 93.8         | 10.8 |
| 165     | 15       | 75.2               | 6.3  | 93           | 14.8 |
| 180     | 15       | 82.8               | 6.6  | 97.8         | 9.8  |
| 195     | 15       | 79.7               | 7.2  | 99.7         | 12.1 |
| 210     | 15       | 82.9               | 7.8  | 99.3         | 12   |
| 225     | 30       | 78.2               | 8.5  | 94.9         | 7.1  |
| 240     | 30       | 80.2               | 7.7  | 93.8         | 7    |
| 255     | 30       | 79.8               | 10.3 | 80.7         | 17.2 |
| 270     | 30       | 86.9               | 9.4  | 100          | 4.6  |
| 285     | 45       | 101.7              | 8.1  | 96.3         | 20.6 |
| 300     | 45       | 105.8              | 6.6  | 92.3         | 17   |
| 315     | 45       | 111.4              | 0.48 | 104.3        | 9.7  |
| 330     | 45       | ND                 | ND   | ND           | ND   |

HVP = Pyrilamine maleate infusion

ND = Not Done

HISTAMINE DOSE-RESPONSE DATA  
Sodium Concentration and Output

| TIME    | DOSE     | Na+ CONCENTRATION |       | SODIUM OUTPUT |       |
|---------|----------|-------------------|-------|---------------|-------|
| minutes | µg/kg-hr | mEq/L             |       | µeq/kg-15min  |       |
|         |          | MEAN              | SEM   | MEAN          | SEM   |
| 15      | 0        | 76.38             | 11.25 | 78.22         | 13.85 |
| 30      | 0        | 77.08             | 10.99 | 65.13         | 12.31 |
| 45      | 0        | 74.35             | 10.20 | 71.21         | 11.86 |
| 60      | HVP      | 73.32             | 9.91  | 65.23         | 9.93  |
| 75      |          | 76.98             | 10.74 | 50.80         | 14.18 |
| 90      |          | 82.03             | 11.41 | 70.35         | 12.85 |
| 105     | 7.5      | 75.64             | 10.46 | 74.06         | 11.18 |
| 120     | 7.5      | 54.93             | 8.95  | 60.80         | 11.04 |
| 135     | 7.5      | 47.96             | 8.49  | 56.17         | 11.25 |
| 150     | 7.5      | 49.58             | 8.84  | 67.29         | 14.16 |
| 165     | 15       | 50.75             | 9.12  | 64.10         | 12.95 |
| 180     | 15       | 46.18             | 8.87  | 56.99         | 12.36 |
| 195     | 15       | 49.90             | 9.27  | 63.97         | 14.41 |
| 210     | 15       | 43.44             | 8.96  | 52.97         | 13.04 |
| 225     | 30       | 46.30             | 10.27 | 59.24         | 14.90 |
| 240     | 30       | 49.28             | 12.19 | 62.50         | 18.25 |
| 255     | 30       | 45.21             | 12.95 | 44.20         | 18.68 |
| 270     | 30       | 40.15             | 13.66 | 51.50         | 21.55 |
| 285     | 45       | 29.58             | 9.38  | 31.26         | 17.33 |
| 300     | 45       | 31.03             | 10.23 | 29.69         | 15.76 |
| 315     | 45       | 23.15             | 2.85  | 21.89         | 4.60  |
| 330     | 45       | ND                | ND    | ND            | ND    |

HVP = Pyrilamine maleate infusion

ND = Not Done

HISTAMINE DOSE-RESPONSE DATA  
Potassium Concentration and Output

| TIME    | DOSE     | K+ CONCENTRATION |      | POTASSIUM OUTPUT |      |
|---------|----------|------------------|------|------------------|------|
| minutes | µg/kg-hr | mEq/L            |      | µeq/kg-15min     |      |
|         |          | MEAN             | SEM  | MEAN             | SEM  |
| 15      | 0        | 7.7              | 1.2  | 7.99             | 1.64 |
| 30      | 0        | 8.3              | 1.3  | 7.38             | 1.9  |
| 45      | 0        | 7.7              | 1.3  | 7.75             | 1.93 |
| 60      | HVP      | 7.1              | 1.04 | 6.38             | 1.26 |
| 75      |          | 5.6              | 0.68 | 3.75             | 1.03 |
| 90      |          | 5.9              | 1    | 5.2              | 1.27 |
| 105     | 7.5      | 8.3              | 1.5  | 8.47             | 2.11 |
| 120     | 7.5      | 10.6             | 1.46 | 12.02            | 2.53 |
| 135     | 7.5      | 9.4              | 1.3  | 10.95            | 2.14 |
| 150     | 7.5      | 10.7             | 1.7  | 14.13            | 3.12 |
| 165     | 15       | 11.4             | 2    | 14.37            | 3.66 |
| 180     | 15       | 12.6             | 2.3  | 15.1             | 3.47 |
| 195     | 15       | 12.5             | 2.3  | 15.75            | 3.39 |
| 210     | 15       | 12.5             | 2.1  | 14.87            | 2.85 |
| 225     | 30       | 10.6             | 2.1  | 12.62            | 2.07 |
| 240     | 30       | 11.2             | 2.3  | 12.94            | 2.3  |
| 255     | 30       | 10.2             | 2.3  | 10.38            | 3.13 |
| 270     | 30       | 11.7             | 3.2  | 13.36            | 3.33 |
| 285     | 45       | 12.6             | 2.4  | 11.5             | 1.16 |
| 300     | 45       | 13.8             | 2.9  | 11.61            | 0.4  |
| 315     | 45       | 12.9             | 2.1  | 11.89            | 0.84 |
| 330     | 45       | ND               | ND   | ND               | ND   |

HVP = Pyrilamine maleate infusion

ND = Not Done

HISTAMINE DOSE-RESPONSE DATA  
Chloride Concentration and Output

| TIME    | DOSE     | CL- CONCENTRATION |      | CHLORIDE OUTPUT |       |
|---------|----------|-------------------|------|-----------------|-------|
| minutes | µg/kg-hr | mEq/L             |      | µeQ/kg-15min    |       |
|         |          | MEAN              | SEM  | MEAN            | SEM   |
| 15      | 0        | 72.87             | 1.15 | 72.19           | 4.85  |
| 30      | 0        | 72.02             | 1.50 | 60.01           | 7.19  |
| 45      | 0        | 71.71             | 1.55 | 67.20           | 7.24  |
| 60      | HVP      | 70.86             | 1.21 | 63.93           | 6.16  |
| 75      |          | 72.45             | 1.23 | 45.91           | 8.77  |
| 90      |          | 69.65             | 2.09 | 58.02           | 3.65  |
| 105     | 7.5      | 74.94             | 2.38 | 72.90           | 5.33  |
| 120     | 7.5      | 77.70             | 2.20 | 84.98           | 8.91  |
| 135     | 7.5      | 76.34             | 2.27 | 86.41           | 7.48  |
| 150     | 7.5      | 77.81             | 0.79 | 101.99          | 10.08 |
| 165     | 15       | 76.48             | 1.58 | 94.74           | 11.49 |
| 180     | 15       | 77.49             | 1.25 | 92.69           | 7.90  |
| 195     | 15       | 76.11             | 1.38 | 95.43           | 7.11  |
| 210     | 15       | 77.83             | 1.36 | 93.72           | 8.10  |
| 225     | 30       | 77.09             | 1.74 | 96.30           | 8.19  |
| 240     | 30       | 76.92             | 1.67 | 92.54           | 9.05  |
| 255     | 30       | 75.78             | 1.90 | 75.53           | 16.06 |
| 270     | 30       | 78.09             | 0.56 | 92.96           | 10.10 |
| 285     | 45       | 75.70             | 3.25 | 72.41           | 17.96 |
| 300     | 45       | 78.50             | 1.50 | 69.20           | 15.65 |
| 315     | 45       | 76.28             | 0.88 | 71.27           | 5.54  |
| 330     | 45       | ND                | ND   | ND              | ND    |

HVP = Pyrilamine maleate infusion

ND = Not Done

APPENDIX B  
PYRILAMINE PRETREATMENT STUDY DATA

| VOLUME (ml) |              |       |                 |        |                    |        |
|-------------|--------------|-------|-----------------|--------|--------------------|--------|
| TIME        | TREATMENT    |       | WITH PYRILAMINE |        | WITHOUT PYRILAMINE |        |
| min         | YES          | NO    | MEAN            | SEM    | MEAN               | SEM    |
| 15          | BASAL        | BASAL | 247.50          | 51.21  | 180.00             | 29.44  |
| 30          | BASAL        | BASAL | 275.00          | 55.75  | 210.00             | 35.36  |
| 45          | BASAL        | BASAL | 300.00          | 20.82  | 297.50             | 62.77  |
| 60          | HVP          | BASAL | 272.50          | 13.15  | 317.50             | 60.05  |
| 75          | P-P          | BASAL | 155.00          | 22.17  | 287.50             | 75.54  |
| 90          | P-P          | BASAL | 187.50          | 52.18  | 330.00             | 82.87  |
| 105         | PENTAGASTRIN |       | 352.50          | 198.80 | 295.00             | 90.60  |
| 120         | PENTAGASTRIN |       | 457.50          | 179.04 | 327.50             | 76.64  |
| 135         | PENTAGASTRIN |       | 435.00          | 203.20 | 432.50             | 110.63 |
| 150         | PENTAGASTRIN |       | 630.00          | 148.72 | 707.50             | 156.86 |
| 165         | PENTAGASTRIN |       | 535.00          | 120.45 | 617.50             | 108.35 |
| 180         | PENTAGASTRIN |       | 602.50          | 131.24 | 627.50             | 69.69  |
| 195         | PENTAGASTRIN |       | ND              | ND     | 590.00             | 72.23  |
| 210         | PENTAGASTRIN |       | ND              | ND     | 650.00             | 101.41 |
| 225         | PENTAGASTRIN |       | ND              | ND     | 667.50             | 102.26 |
| 240         | PENTAGASTRIN |       | ND              | ND     | 645.00             | 41.33  |

YES = Pyrilamine Maleate Pretreatment

NO = No Pretreatment

ND = Not Done

HVP = Pyrilamine infusion

P-P = Post-Pyrilamine

## PYRILAMINE PRETREATMENT STUDY DATA

| ACID CONCENTRATION (mEq/L) |              |       |                 |       |                    |       |
|----------------------------|--------------|-------|-----------------|-------|--------------------|-------|
| TIME                       | PRETREATMENT |       | WITH PYRILAMINE |       | WITHOUT PYRILAMINE |       |
| min                        | YES          | NO    | MEAN            | SEM   | MEAN               | SEM   |
| 15                         | BASAL        | BASAL | 40.25           | 12.69 | 27.15              | 16.06 |
| 30                         | BASAL        | BASAL | 40.15           | 10.14 | 22.20              | 15.65 |
| 45                         | BASAL        | BASAL | 38.78           | 8.43  | 28.69              | 16.29 |
| 60                         | HVP          | BASAL | 37.85           | 10.33 | 30.58              | 10.32 |
| 75                         | P-P          | BASAL | 38.61           | 7.90  | 37.90              | 13.30 |
| 90                         | P-P          | BASAL | 26.00           | 5.99  | 32.11              | 13.50 |
| 105                        | PENTAGASTRIN |       | 26.36           | 12.53 | 38.09              | 14.55 |
| 120                        | PENTAGASTRIN |       | 37.46           | 17.04 | 34.95              | 12.28 |
| 135                        | PENTAGASTRIN |       | 45.45           | 19.60 | 28.71              | 14.98 |
| 150                        | PENTAGASTRIN |       | 49.89           | 18.06 | 27.75              | 5.37  |
| 165                        | PENTAGASTRIN |       | 54.91           | 15.54 | 37.05              | 8.02  |
| 180                        | PENTAGASTRIN |       | 49.86           | 13.01 | 47.00              | 10.51 |
| 195                        | PENTAGASTRIN |       | ND              | ND    | 50.66              | 9.84  |
| 210                        | PENTAGASTRIN |       | ND              | ND    | 46.25              | 11.38 |
| 225                        | PENTAGASTRIN |       | ND              | ND    | 45.01              | 10.37 |
| 240                        | PENTAGASTRIN |       | ND              | ND    | 43.76              | 4.85  |

YES = Pyrilamine Maleate Pretreatment

NO = No Pretreatment

ND = Not Done

HVP = Pyrilamine infusion

P-P = Post-Pyrilamine

## PYRILAMINE PRETREATMENT STUDY DATA

| ACID OUTPUT ( $\mu$ Eq/kg-15 min) |              |       |                 |       |                    |       |
|-----------------------------------|--------------|-------|-----------------|-------|--------------------|-------|
| TIME                              | PRETREATMENT |       | WITH PYRILAMINE |       | WITHOUT PYRILAMINE |       |
| min                               | YES          | NO    | MEAN            | SEM   | MEAN               | SEM   |
| 15                                | BASAL        | BASAL | 21.01           | 8.14  | 11.22              | 6.23  |
| 30                                | BASAL        | BASAL | 22.96           | 6.33  | 12.63              | 8.70  |
| 45                                | BASAL        | BASAL | 26.01           | 5.34  | 16.91              | 8.60  |
| 60                                | HVP          | BASAL | 23.28           | 5.81  | 21.62              | 7.86  |
| 75                                | P-P          | BASAL | 13.65           | 2.93  | 25.26              | 10.99 |
| 90                                | P-P          | BASAL | 10.49           | 2.63  | 29.02              | 10.83 |
| 105                               | PENTAGASTRIN |       | 12.33           | 4.91  | 34.37              | 11.61 |
| 120                               | PENTAGASTRIN |       | 32.59           | 10.20 | 35.64              | 12.52 |
| 135                               | PENTAGASTRIN |       | 35.23           | 12.93 | 35.47              | 14.39 |
| 150                               | PENTAGASTRIN |       | 54.67           | 10.46 | 46.96              | 5.93  |
| 165                               | PENTAGASTRIN |       | 56.43           | 6.69  | 56.64              | 7.58  |
| 180                               | PENTAGASTRIN |       | 58.40           | 4.55  | 77.53              | 12.48 |
| 195                               | PENTAGASTRIN |       | ND              | ND    | 77.90              | 9.28  |
| 210                               | PENTAGASTRIN |       | ND              | ND    | 74.98              | 10.13 |
| 225                               | PENTAGASTRIN |       | ND              | ND    | 76.32              | 10.87 |
| 240                               | PENTAGASTRIN |       | ND              | ND    | 78.40              | 9.56  |

YES = Pyrilamine Maleate Pretreatment

NO = No Pretreatment

ND = Not Done

HVP = Pyrilamine infusion

P-P = Post-Pyrilamine

APPENDIX C  
DATA FROM BALLOON/NO BALLOON STUDY

Volume of Gastric Contents

(ml/15 minutes)

No Balloon

| TIME<br>min | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|-------------|-----------|--------|-------|-----------|-------|--------------|-------|
|             |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15          | BASAL     | 490.0  | 44.12 | 497.5     | 60.63 | 523.3        | 49.12 |
| 30          | BASAL     | 420.8  | 54.93 | 464.3     | 68.79 | 541.7        | 45.20 |
| 45          | BASAL     | 405.8  | 56.12 | 422.5     | 82.52 | 541.7        | 42.93 |
| 60          | HVP       | 429.5  | 71.64 | 439.2     | 53.87 | 470.8        | 34.84 |
| 75          |           | 350.5  | 61.29 | 328.3     | 46.72 | 409.8        | 55.93 |
| 90          |           | 361.7  | 45.86 | 335.8     | 60.27 | 383.3        | 36.46 |
| 105         | INFUSION  | 393.3  | 74.37 | 419.2     | 40.38 | 505.8        | 70.36 |
| 120         | INFUSION  | 456.8  | 58.95 | 569.2     | 52.26 | 800.8        | 74.17 |
| 135         | INFUSION  | 493.3  | 27.89 | 598.3     | 52.75 | 899.2        | 62.67 |
| 150         | INFUSION  | 491.7  | 22.42 | 665.0     | 49.58 | 923.3        | 41.20 |
| 165         | INFUSION  | 465.8  | 21.85 | 650.8     | 49.27 | 886.7        | 38.36 |
| 180         | INFUSION  | 480.0  | 39.24 | 677.5     | 53.69 | 885.0        | 40.72 |

HVP = Pyrilamine maleate infusion

## Volume of Gastric Contents

(ml/15minutes)

Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|------|-----------|--------|-------|-----------|-------|--------------|-------|
| min  |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15   | BASAL     | 272.0  | 45.13 | 266.2     | 56.27 | 229.5        | 46.22 |
| 30   | BASAL     | 245.5  | 53.38 | 246.7     | 69.62 | 251.0        | 34.30 |
| 45   | BASAL     | 252.3  | 40.58 | 251.5     | 58.20 | 259.0        | 37.07 |
| 60   | HVP       | 194.7  | 36.72 | 237.7     | 54.05 | 233.3        | 26.09 |
| 75   |           | 139.3  | 31.75 | 148.2     | 33.19 | 164.0        | 27.99 |
| 90   |           | 138.0  | 24.72 | 170.0     | 35.33 | 163.7        | 27.86 |
| 105  | INFUSION  | 200.0  | 29.34 | 207.7     | 49.00 | 269.7        | 26.40 |
| 120  | INFUSION  | 215.0  | 33.74 | 299.2     | 77.17 | 427.5        | 39.99 |
| 135  | INFUSION  | 211.7  | 29.67 | 326.3     | 54.89 | 468.3        | 24.45 |
| 150  | INFUSION  | 219.3  | 31.58 | 386.8     | 61.57 | 450.0        | 26.61 |
| 165  | INFUSION  | 233.2  | 39.58 | 436.0     | 53.74 | 550.0        | 66.72 |
| 180  | INFUSION  | 220.7  | 45.42 | 455.0     | 58.30 | 497.5        | 38.03 |

HVP = Pyrilamine maleate infusion

## pH of Gastric Contents

No Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|------|-----------|--------|-------|-----------|-------|--------------|-------|
| min  |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15   | BASAL     | 2.37   | 0.792 | 1.67      | 0.167 | 2.71         | 0.927 |
| 30   | BASAL     | 2.39   | 0.839 | 1.55      | 0.055 | 2.39         | 0.629 |
| 45   | BASAL     | 2.69   | 1.044 | 1.73      | 0.136 | 1.83         | 0.148 |
| 60   | HVP       | 2.67   | 1.106 | 2.53      | 0.835 | 1.70         | 0.088 |
| 75   |           | 2.68   | 0.966 | 2.40      | 0.790 | 1.69         | 0.073 |
| 90   |           | 3.05   | 1.062 | 2.69      | 0.699 | 2.07         | 0.257 |
| 105  | INFUSION  | 2.91   | 1.008 | 1.72      | 0.130 | 3.46         | 0.869 |
| 120  | INFUSION  | 2.81   | 0.894 | 1.36      | 0.050 | 2.90         | 0.810 |
| 135  | INFUSION  | 2.73   | 0.758 | 1.33      | 0.060 | 1.85         | 0.136 |
| 150  | INFUSION  | 2.34   | 0.447 | 1.34      | 0.056 | 1.67         | 0.062 |
| 165  | INFUSION  | 2.48   | 0.719 | 1.32      | 0.055 | 1.61         | 0.047 |
| 180  | INFUSION  | 2.42   | 0.673 | 1.34      | 0.084 | 1.57         | 0.052 |

HVP = Pyrilamine maleate infusion

## pH of Gastric Contents

Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|------|-----------|--------|-------|-----------|-------|--------------|-------|
|      |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15   | BASAL     | 1.59   | 0.124 | 1.77      | 0.164 | 2.38         | 0.904 |
| 30   | BASAL     | 1.52   | 0.095 | 2.00      | 0.407 | 1.54         | 0.131 |
| 45   | BASAL     | 1.54   | 0.094 | 2.93      | 0.940 | 2.18         | 0.778 |
| 60   | HVP       | 1.72   | 0.208 | 3.49      | 1.259 | 2.45         | 1.060 |
| 75   |           | 2.04   | 0.343 | 3.56      | 1.217 | 2.53         | 1.072 |
| 90   |           | 2.23   | 0.419 | 2.89      | 0.962 | 2.59         | 1.083 |
| 105  | INFUSION  | 2.77   | 0.726 | 1.90      | 0.269 | 1.52         | 0.109 |
| 120  | INFUSION  | 2.40   | 0.743 | 1.33      | 0.040 | 1.32         | 0.028 |
| 135  | INFUSION  | 2.35   | 0.783 | 1.25      | 0.020 | 1.26         | 0.034 |
| 150  | INFUSION  | 2.62   | 0.895 | 1.23      | 0.026 | 1.27         | 0.031 |
| 165  | INFUSION  | 2.47   | 0.888 | 1.22      | 0.033 | 1.28         | 0.028 |
| 180  | INFUSION  | 2.42   | 0.926 | 1.20      | 0.041 | 1.26         | 0.022 |

HVP = Pyrilamine maleate infusion

## Potassium Concentration in Gastric Contents

(mEq/L)

No Balloon

| TIME | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|------|-----------|--------|------|-----------|------|--------------|------|
| min  |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15   | BASAL     | 11.67  | 1.09 | 10.76     | 0.92 | 9.97         | 0.91 |
| 30   | BASAL     | 10.88  | 1.05 | 9.73      | 0.77 | 9.76         | 0.76 |
| 45   | BASAL     | 10.55  | 1.25 | 8.32      | 0.97 | 9.65         | 0.69 |
| 60   | HVP       | 10.38  | 1.07 | 7.91      | 0.82 | 9.76         | 0.77 |
| 75   |           | 8.89   | 0.81 | 7.60      | 0.54 | 8.62         | 0.54 |
| 90   |           | 8.38   | 1.00 | 7.44      | 0.50 | 7.63         | 0.44 |
| 105  | INFUSION  | 9.28   | 0.72 | 10.16     | 0.87 | 7.82         | 0.38 |
| 120  | INFUSION  | 9.31   | 0.52 | 14.43     | 0.85 | 9.78         | 0.81 |
| 135  | INFUSION  | 9.68   | 0.80 | 14.87     | 0.98 | 10.03        | 0.61 |
| 150  | INFUSION  | 9.78   | 0.85 | 14.19     | 0.86 | 10.49        | 0.42 |
| 165  | INFUSION  | 9.68   | 0.50 | 14.08     | 0.79 | 10.01        | 0.40 |
| 180  | INFUSION  | 9.97   | 0.78 | 13.95     | 1.01 | 10.66        | 0.66 |

HVP = Pyrilamine maleate infusion

## Potassium Concentration in Gastric Contents

(mEq/L)

Balloon

| TIME | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|------|-----------|--------|------|-----------|------|--------------|------|
| min  |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15   | BASAL     | 11.07  | 1.60 | 9.14      | 1.17 | 9.97         | 1.54 |
| 30   | BASAL     | 9.84   | 1.09 | 9.69      | 1.25 | 10.44        | 1.45 |
| 45   | BASAL     | 9.04   | 0.92 | 9.44      | 1.27 | 10.40        | 1.19 |
| 60   | HVP       | 8.73   | 1.08 | 8.58      | 1.08 | 10.74        | 1.11 |
| 75   |           | 7.52   | 0.91 | 6.87      | 0.56 | 8.52         | 0.73 |
| 90   |           | 7.34   | 0.95 | 7.31      | 0.65 | 8.33         | 0.69 |
| 105  | INFUSION  | 9.25   | 1.40 | 10.56     | 1.08 | 11.26        | 1.10 |
| 120  | INFUSION  | 9.90   | 1.32 | 17.70     | 0.84 | 13.99        | 1.35 |
| 135  | INFUSION  | 9.95   | 1.54 | 18.62     | 1.03 | 14.81        | 1.30 |
| 150  | INFUSION  | 9.45   | 1.00 | 18.21     | 0.95 | 13.88        | 1.15 |
| 165  | INFUSION  | 9.06   | 0.95 | 18.11     | 1.03 | 13.12        | 1.06 |
| 180  | INFUSION  | 8.80   | 1.16 | 17.20     | 1.03 | 13.44        | 1.01 |

HVP = Pyrilamine maleate infusion

## Potassium Output in Gastric Contents

(μEq/kg/15minutes)

No Balloon

| TIME | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|------|-----------|--------|------|-----------|------|--------------|------|
| min  |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15   | BASAL     | 12.24  | 1.85 | 11.24     | 1.54 | 11.33        | 1.82 |
| 30   | BASAL     | 10.16  | 2.39 | 10.02     | 1.98 | 11.53        | 1.73 |
| 45   | BASAL     | 9.67   | 2.22 | 8.26      | 2.31 | 11.42        | 1.75 |
| 60   | HVP       | 10.11  | 2.34 | 7.75      | 1.67 | 9.91         | 1.33 |
| 75   |           | 6.70   | 1.40 | 5.21      | 0.75 | 7.84         | 1.47 |
| 90   |           | 6.65   | 1.27 | 5.40      | 1.22 | 6.37         | 0.93 |
| 105  | INFUSION  | 7.96   | 1.88 | 9.07      | 1.24 | 8.54         | 1.39 |
| 120  | INFUSION  | 9.06   | 1.39 | 17.36     | 1.62 | 16.72        | 2.03 |
| 135  | INFUSION  | 10.19  | 1.13 | 18.57     | 1.18 | 18.94        | 1.02 |
| 150  | INFUSION  | 10.29  | 1.23 | 19.81     | 1.14 | 20.64        | 1.21 |
| 165  | INFUSION  | 9.54   | 0.55 | 19.28     | 1.21 | 18.90        | 1.02 |
| 180  | INFUSION  | 10.06  | 0.95 | 19.77     | 1.33 | 20.13        | 1.59 |

HVP = Pyrilamine maleate infusion

## Potassium Output in Gastric Contents

(μEq/kg/15minutes)

Balloon

| TIME | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|------|-----------|--------|------|-----------|------|--------------|------|
| min  |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15   | BASAL     | 6.64   | 1.49 | 5.74      | 1.91 | 5.17         | 1.32 |
| 30   | BASAL     | 5.21   | 1.20 | 5.92      | 2.04 | 5.88         | 1.21 |
| 45   | BASAL     | 4.90   | 0.92 | 5.68      | 1.78 | 5.89         | 1.10 |
| 60   | HVP       | 3.56   | 0.74 | 4.83      | 1.51 | 5.45         | 0.94 |
| 75   |           | 2.16   | 0.55 | 2.19      | 0.50 | 2.78         | 0.35 |
| 90   |           | 2.15   | 0.44 | 2.65      | 0.60 | 2.93         | 0.53 |
| 105  | INFUSION  | 3.88   | 0.74 | 4.90      | 1.47 | 6.55         | 1.06 |
| 120  | INFUSION  | 4.60   | 0.99 | 11.08     | 2.51 | 12.55        | 1.67 |
| 135  | INFUSION  | 4.49   | 0.90 | 12.69     | 1.79 | 14.41        | 0.68 |
| 150  | INFUSION  | 4.36   | 0.83 | 14.64     | 1.91 | 13.00        | 0.73 |
| 165  | INFUSION  | 4.48   | 0.90 | 16.55     | 1.84 | 15.22        | 2.29 |
| 180  | INFUSION  | 4.26   | 1.23 | 16.19     | 1.60 | 14.09        | 1.49 |

HVP = Pyrilamine maleate infusion

## Chloride Concentration in Gastric Contents

(mEq/L)

No Balloon

| TIME<br>min | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|-------------|-----------|--------|------|-----------|------|--------------|------|
|             |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15          | BASAL     | 139.3  | 4.24 | 133.9     | 5.04 | 140.2        | 6.07 |
| 30          | BASAL     | 144.5  | 4.91 | 135.9     | 7.54 | 148.3        | 4.71 |
| 45          | BASAL     | 144.0  | 5.59 | 137.0     | 4.76 | 150.8        | 5.98 |
| 60          | HVP       | 147.2  | 4.63 | 137.8     | 7.93 | 151.2        | 5.70 |
| 75          |           | 142.5  | 4.84 | 136.9     | 8.94 | 150.3        | 5.34 |
| 90          |           | 142.6  | 5.66 | 138.0     | 6.63 | 148.0        | 6.50 |
| 105         | INFUSION  | 146.1  | 7.90 | 145.0     | 6.08 | 134.4        | 7.84 |
| 120         | INFUSION  | 147.5  | 4.80 | 143.6     | 5.54 | 144.9        | 5.06 |
| 135         | INFUSION  | 146.2  | 5.19 | 144.4     | 4.43 | 143.2        | 5.51 |
| 150         | INFUSION  | 141.2  | 4.95 | 147.0     | 3.45 | 144.7        | 3.87 |
| 165         | INFUSION  | 143.1  | 4.02 | 143.3     | 4.50 | 143.5        | 5.65 |
| 180         | INFUSION  | 143.4  | 3.62 | 146.5     | 2.74 | 144.5        | 7.71 |

HVP = Pyrilamine maleate infusion

## Chloride Concentration in Gastric Contents

(mEq/L)

Balloon

| TIME<br>min | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|-------------|-----------|--------|------|-----------|------|--------------|------|
|             |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15          | BASAL     | 151.1  | 3.08 | 148.8     | 4.56 | 149.5        | 6.68 |
| 30          | BASAL     | 152.2  | 3.72 | 151.2     | 3.07 | 151.0        | 6.54 |
| 45          | BASAL     | 150.9  | 3.22 | 152.3     | 7.46 | 149.0        | 7.34 |
| 60          | HVP       | 151.2  | 4.80 | 155.4     | 7.89 | 145.8        | 4.11 |
| 75          |           | 148.5  | 4.72 | 160.9     | 6.01 | 146.7        | 5.79 |
| 90          |           | 149.1  | 4.84 | 167.6     | 5.10 | 147.4        | 6.99 |
| 105         | INFUSION  | 149.7  | 4.78 | 162.0     | 4.15 | 147.8        | 3.70 |
| 120         | INFUSION  | 148.8  | 5.79 | 165.4     | 3.68 | 156.5        | 4.60 |
| 135         | INFUSION  | 150.3  | 4.43 | 159.4     | 5.31 | 149.0        | 3.04 |
| 150         | INFUSION  | 151.0  | 6.58 | 153.6     | 5.87 | 151.7        | 3.69 |
| 165         | INFUSION  | 151.8  | 4.77 | 156.4     | 2.70 | 153.6        | 2.64 |
| 180         | INFUSION  | 150.7  | 5.37 | 157.5     | 4.37 | 154.5        | 2.47 |

HVP = Pyrilamine maleate infusion

## Chloride Output in Gastric Contents

(μEq/kg/15minutes)

No Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|------|-----------|--------|-------|-----------|-------|--------------|-------|
|      |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15   | BASAL     | 144.8  | 13.33 | 143.8     | 21.01 | 156.3        | 17.09 |
| 30   | BASAL     | 131.3  | 20.66 | 136.3     | 24.94 | 136.3        | 24.94 |
| 45   | BASAL     | 127.2  | 22.11 | 127.7     | 27.93 | 174.3        | 15.53 |
| 60   | HVP       | 137.2  | 25.79 | 131.8     | 22.06 | 151.9        | 14.06 |
| 75   |           | 107.0  | 21.14 | 95.9      | 17.18 | 134.9        | 21.76 |
| 90   |           | 109.9  | 15.54 | 98.2      | 19.95 | 120.6        | 11.46 |
| 105  | INFUSION  | 119.9  | 24.13 | 131.5     | 16.56 | 145.8        | 23.74 |
| 120  | INFUSION  | 139.8  | 14.24 | 176.2     | 18.91 | 245.7        | 18.13 |
| 135  | INFUSION  | 152.6  | 8.15  | 185.2     | 18.92 | 277.9        | 30.20 |
| 150  | INFUSION  | 147.1  | 6.86  | 210.4     | 20.33 | 287.4        | 22.51 |
| 165  | INFUSION  | 141.3  | 6.74  | 200.8     | 20.12 | 272.9        | 20.35 |
| 180  | INFUSION  | 145.2  | 10.89 | 213.8     | 20.78 | 272.9        | 18.58 |

HVP = Pyrilamine maleate infusion

## Chloride Output in Gastric Contents

(μEq/kg/15minutes)

Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|------|-----------|--------|-------|-----------|-------|--------------|-------|
| min  |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15   | BASAL     | 88.2   | 15.26 | 87.2      | 19.95 | 73.1         | 15.61 |
| 30   | BASAL     | 79.8   | 17.74 | 82.0      | 23.35 | 82.4         | 13.43 |
| 45   | BASAL     | 81.9   | 13.99 | 83.2      | 19.33 | 83.6         | 13.72 |
| 60   | HVP       | 64.3   | 13.67 | 80.5      | 19.12 | 73.2         | 9.44  |
| 75   |           | 45.8   | 11.54 | 51.2      | 11.59 | 51.5         | 9.49  |
| 90   |           | 44.7   | 8.84  | 59.7      | 10.71 | 52.9         | 10.47 |
| 105  | INFUSION  | 64.4   | 10.03 | 70.9      | 16.58 | 84.3         | 7.42  |
| 120  | INFUSION  | 69.1   | 11.47 | 105.0     | 27.41 | 141.9        | 13.99 |
| 135  | INFUSION  | 68.6   | 10.79 | 111.2     | 20.15 | 147.7        | 6.90  |
| 150  | INFUSION  | 70.8   | 11.25 | 128.4     | 23.24 | 144.5        | 8.56  |
| 165  | INFUSION  | 75.8   | 13.35 | 145.6     | 19.32 | 180.0        | 23.38 |
| 180  | INFUSION  | 71.7   | 14.79 | 152.7     | 19.74 | 164.0        | 14.75 |

HVP = Pyrilamine maleate infusion

## Acid Concentration in Gastric Contents

(mEq/L)

No Balloon

| TIME | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|------|-----------|--------|------|-----------|------|--------------|------|
| min  |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15   | BASAL     | 37.4   | 7.52 | 40.8      | 7.40 | 26.5         | 7.61 |
| 30   | BASAL     | 38.2   | 6.73 | 41.8      | 4.39 | 25.1         | 6.65 |
| 45   | BASAL     | 35.2   | 9.27 | 34.3      | 6.65 | 27.9         | 5.49 |
| 60   | HVP       | 37.7   | 8.25 | 29.1      | 9.23 | 32.5         | 4.99 |
| 75   |           | 31.8   | 7.06 | 32.6      | 9.30 | 32.9         | 2.71 |
| 90   |           | 22.2   | 7.44 | 21.6      | 7.20 | 24.8         | 5.82 |
| 105  | INFUSION  | 22.6   | 6.58 | 35.9      | 6.59 | 16.6         | 4.52 |
| 120  | INFUSION  | 23.2   | 6.32 | 71.2      | 4.64 | 24.1         | 5.90 |
| 135  | INFUSION  | 21.9   | 5.56 | 81.0      | 5.96 | 30.5         | 5.37 |
| 150  | INFUSION  | 24.5   | 7.19 | 77.7      | 5.56 | 35.7         | 3.59 |
| 165  | INFUSION  | 29.0   | 5.51 | 78.0      | 4.53 | 40.1         | 2.90 |
| 180  | INFUSION  | 28.8   | 5.43 | 82.7      | 5.18 | 44.7         | 3.38 |

HVP = Pyrilamine maleate infusion

## Acid Concentration in Gastric Contents

(mEq/L)

Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|------|-----------|--------|-------|-----------|-------|--------------|-------|
|      |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15   | BASAL     | 53.3   | 9.93  | 37.8      | 9.37  | 46.9         | 12.28 |
| 30   | BASAL     | 53.9   | 9.84  | 40.1      | 10.79 | 52.4         | 8.95  |
| 45   | BASAL     | 48.6   | 7.96  | 35.8      | 12.98 | 51.1         | 10.41 |
| 60   | HVP       | 44.2   | 10.13 | 33.8      | 13.03 | 53.5         | 10.97 |
| 75   |           | 34.9   | 9.16  | 28.8      | 12.79 | 44.5         | 9.29  |
| 90   |           | 27.1   | 7.73  | 22.8      | 8.82  | 38.9         | 8.13  |
| 105  | INFUSION  | 27.0   | 8.34  | 39.7      | 11.10 | 50.8         | 7.52  |
| 120  | INFUSION  | 34.0   | 8.61  | 85.4      | 6.65  | 73.6         | 5.09  |
| 135  | INFUSION  | 39.3   | 9.89  | 96.0      | 3.93  | 85.6         | 2.59  |
| 150  | INFUSION  | 39.1   | 11.03 | 101.1     | 3.37  | 85.2         | 4.23  |
| 165  | INFUSION  | 38.4   | 9.88  | 102.1     | 3.76  | 82.2         | 5.22  |
| 180  | INFUSION  | 39.1   | 8.30  | 104.2     | 3.21  | 86.1         | 4.66  |

HVP = Pyrilamine maleate infusion

## Acid Output in Gastric Contents

(μEq/kg/15minutes)

No Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|------|-----------|--------|-------|-----------|-------|--------------|-------|
|      |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15   | BASAL     | 38.4   | 9.03  | 42.4      | 9.53  | 31.0         | 10.00 |
| 30   | BASAL     | 36.1   | 10.09 | 42.3      | 9.50  | 29.9         | 9.07  |
| 45   | BASAL     | 34.7   | 11.53 | 35.9      | 12.09 | 34.0         | 9.09  |
| 60   | HVP       | 39.5   | 11.10 | 31.0      | 12.55 | 34.2         | 7.87  |
| 75   |           | 25.8   | 8.35  | 24.4      | 9.93  | 29.1         | 5.01  |
| 90   |           | 17.7   | 7.01  | 17.1      | 8.95  | 20.8         | 5.35  |
| 105  | INFUSION  | 18.6   | 8.29  | 33.5      | 9.01  | 18.9         | 6.64  |
| 120  | INFUSION  | 21.7   | 7.36  | 86.9      | 10.36 | 41.4         | 10.44 |
| 135  | INFUSION  | 23.1   | 6.47  | 100.9     | 6.59  | 56.7         | 10.15 |
| 150  | INFUSION  | 26.2   | 8.64  | 108.0     | 6.04  | 69.7         | 6.59  |
| 165  | INFUSION  | 28.3   | 5.33  | 107.5     | 8.46  | 75.7         | 6.25  |
| 180  | INFUSION  | 28.8   | 5.69  | 117.8     | 8.16  | 84.7         | 7.74  |

HVP = Pyrilamine maleate infusion

## Acid Output in Gastric Contents

(μEq/kg/15minutes)

Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |      |
|------|-----------|--------|-------|-----------|-------|--------------|------|
| min  |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM  |
| 15   | BASAL     | 34.4   | 9.91  | 26.2      | 11.94 | 26.9         | 8.50 |
| 30   | BASAL     | 32.1   | 10.71 | 28.6      | 13.47 | 30.1         | 5.80 |
| 45   | BASAL     | 28.4   | 7.81  | 27.0      | 13.07 | 30.9         | 6.34 |
| 60   | HVP       | 19.8   | 7.15  | 24.1      | 11.66 | 28.9         | 6.06 |
| 75   |           | 11.9   | 5.09  | 13.0      | 8.02  | 16.3         | 3.62 |
| 90   |           | 9.5    | 3.95  | 11.1      | 6.10  | 14.9         | 4.05 |
| 105  | INFUSION  | 12.7   | 4.15  | 21.8      | 9.64  | 30.9         | 6.41 |
| 120  | INFUSION  | 17.8   | 5.01  | 56.7      | 16.94 | 66.5         | 7.33 |
| 135  | INFUSION  | 20.1   | 5.49  | 68.1      | 12.82 | 84.9         | 4.36 |
| 150  | INFUSION  | 19.6   | 6.50  | 82.8      | 12.28 | 80.8         | 4.73 |
| 165  | INFUSION  | 22.1   | 7.22  | 94.1      | 10.43 | 92.9         | 6.68 |
| 180  | INFUSION  | 21.4   | 6.76  | 100.0     | 11.22 | 89.5         | 5.02 |

HVP = Pyrilamine maleate infusion

## Sodium Concentration in Gastric Contents

(mEq/L)

No Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |      | PENTAGASTRIN |      |
|------|-----------|--------|-------|-----------|------|--------------|------|
| min  |           | Mean   | SEM   | Mean      | SEM  | Mean         | SEM  |
| 15   | BASAL     | 104.9  | 5.98  | 89.0      | 6.38 | 105.1        | 9.96 |
| 30   | BASAL     | 103.1  | 7.52  | 88.5      | 5.40 | 109.5        | 9.80 |
| 45   | BASAL     | 109.5  | 11.91 | 94.1      | 6.76 | 104.2        | 7.54 |
| 60   | HVP       | 105.3  | 10.98 | 98.9      | 8.58 | 100.4        | 6.57 |
| 75   |           | 113.1  | 8.43  | 94.6      | 7.16 | 100.7        | 2.87 |
| 90   |           | 120.5  | 7.27  | 107.0     | 5.19 | 106.2        | 5.58 |
| 105  | INFUSION  | 119.3  | 6.61  | 91.3      | 6.24 | 109.8        | 5.51 |
| 120  | INFUSION  | 111.8  | 5.46  | 60.0      | 4.87 | 105.0        | 6.79 |
| 135  | INFUSION  | 115.1  | 4.96  | 49.9      | 6.30 | 96.4         | 6.44 |
| 150  | INFUSION  | 111.5  | 5.10  | 53.6      | 5.93 | 94.4         | 5.05 |
| 165  | INFUSION  | 107.9  | 4.22  | 55.1      | 4.76 | 86.8         | 4.72 |
| 180  | INFUSION  | 108.1  | 5.05  | 49.9      | 5.68 | 89.5         | 4.83 |

HVP = Pyrilamine maleate infusion

## Sodium Concentration in Gastric Contents

(mEq/L)

Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|------|-----------|--------|-------|-----------|-------|--------------|-------|
| min  |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15   | BASAL     | 82.9   | 9.98  | 99.2      | 9.54  | 86.0         | 12.47 |
| 30   | BASAL     | 79.9   | 10.11 | 97.8      | 10.02 | 80.6         | 7.77  |
| 45   | BASAL     | 87.2   | 8.80  | 101.3     | 11.59 | 79.7         | 7.87  |
| 60   | HVP       | 91.3   | 10.21 | 105.5     | 12.21 | 79.9         | 8.44  |
| 75   |           | 93.6   | 9.62  | 106.2     | 12.18 | 88.7         | 8.49  |
| 90   |           | 102.8  | 8.90  | 115.2     | 10.43 | 94.9         | 9.67  |
| 105  | INFUSION  | 100.6  | 8.95  | 97.7      | 13.97 | 83.2         | 7.77  |
| 120  | INFUSION  | 95.0   | 8.32  | 48.8      | 6.56  | 62.5         | 6.43  |
| 135  | INFUSION  | 91.9   | 9.28  | 35.6      | 3.42  | 52.9         | 5.07  |
| 150  | INFUSION  | 88.7   | 9.41  | 31.4      | 3.79  | 54.1         | 5.94  |
| 165  | INFUSION  | 92.0   | 9.39  | 31.7      | 4.39  | 56.6         | 7.70  |
| 180  | INFUSION  | 91.2   | 9.68  | 30.5      | 3.92  | 52.9         | 6.96  |

HVP = Pyrilamine maleate infusion

## Sodium Output in Gastric Contents

(μEq/kg/15minutes)

No Balloon

| TIME<br>min | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|-------------|-----------|--------|-------|-----------|-------|--------------|-------|
|             |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15          | BASAL     | 109.0  | 11.10 | 95.5      | 13.84 | 113.7        | 8.50  |
| 30          | BASAL     | 91.0   | 11.35 | 87.8      | 14.97 | 126.2        | 16.00 |
| 45          | BASAL     | 90.5   | 10.05 | 81.8      | 14.55 | 118.0        | 6.73  |
| 60          | HVP       | 92.7   | 15.30 | 90.8      | 11.55 | 98.5         | 3.46  |
| 75          |           | 83.6   | 14.13 | 65.6      | 10.22 | 89.9         | 14.66 |
| 90          |           | 92.2   | 12.04 | 75.8      | 12.91 | 86.2         | 8.24  |
| 105         | INFUSION  | 100.0  | 18.79 | 81.3      | 8.78  | 114.7        | 11.91 |
| 120         | INFUSION  | 108.9  | 15.11 | 73.1      | 8.47  | 178.1        | 16.21 |
| 135         | INFUSION  | 120.3  | 7.38  | 67.6      | 12.77 | 186.3        | 20.53 |
| 150         | INFUSION  | 115.9  | 5.01  | 79.3      | 13.57 | 187.6        | 17.53 |
| 165         | INFUSION  | 106.9  | 6.69  | 78.8      | 12.33 | 165.2        | 14.37 |
| 180         | INFUSION  | 110.8  | 10.91 | 75.3      | 13.48 | 169.7        | 15.00 |

HVP = Pyrilamine maleate infusion

## Sodium Output in Gastric Contents

(μEq/kg/15minutes)

Balloon

| TIME | TREATMENT | SALINE |      | HISTAMINE |       | PENTAGASTRIN |       |
|------|-----------|--------|------|-----------|-------|--------------|-------|
| min  |           | Mean   | SEM  | Mean      | SEM   | Mean         | SEM   |
| 15   | BASAL     | 43.7   | 4.19 | 53.7      | 9.51  | 38.0         | 6.96  |
| 30   | BASAL     | 36.6   | 3.82 | 46.4      | 10.49 | 42.1         | 6.98  |
| 45   | BASAL     | 43.9   | 5.29 | 48.4      | 7.26  | 42.3         | 6.51  |
| 60   | HVP       | 35.7   | 6.63 | 46.8      | 5.68  | 38.6         | 5.21  |
| 75   |           | 26.7   | 6.13 | 29.7      | 2.94  | 30.0         | 5.25  |
| 90   |           | 28.2   | 3.12 | 38.4      | 4.58  | 33.3         | 6.34  |
| 105  | INFUSION  | 41.1   | 5.55 | 37.5      | 4.55  | 46.6         | 4.51  |
| 120  | INFUSION  | 40.7   | 4.48 | 29.1      | 6.46  | 58.0         | 10.44 |
| 135  | INFUSION  | 38.6   | 2.96 | 23.7      | 3.87  | 52.2         | 5.34  |
| 150  | INFUSION  | 40.0   | 6.23 | 26.9      | 6.67  | 51.4         | 5.84  |
| 165  | INFUSION  | 42.6   | 5.33 | 30.1      | 6.56  | 71.6         | 21.33 |
| 180  | INFUSION  | 40.0   | 7.27 | 30.1      | 6.65  | 58.8         | 12.68 |

HVP = Pyrilamine maleate infusion

## Volume of Duodenal Contents

(ml/15minutes)

No Balloon

| TIME | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|------|-----------|--------|-------|-----------|-------|--------------|-------|
|      |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15   | BASAL     | 123.0  | 22.27 | 28.7      | 9.81  | 29.0         | 13.71 |
| 30   | BASAL     | 89.7   | 32.49 | 65.7      | 34.39 | 26.2         | 12.29 |
| 45   | BASAL     | 118.3  | 38.62 | 56.5      | 27.10 | 29.2         | 10.34 |
| 60   | HVP       | 111.0  | 24.69 | 42.4      | 25.67 | 28.0         | 10.73 |
| 75   |           | 96.3   | 30.22 | 63.3      | 10.02 | 28.8         | 9.22  |
| 90   |           | 85.7   | 28.71 | 82.8      | 20.57 | 29.8         | 10.76 |
| 105  | INFUSION  | 93.5   | 36.58 | 73.7      | 23.30 | 79.7         | 25.35 |
| 120  | INFUSION  | 73.7   | 39.04 | 87.0      | 28.56 | 87.0         | 16.94 |
| 135  | INFUSION  | 63.0   | 20.85 | 93.3      | 41.51 | 79.3         | 18.03 |
| 150  | INFUSION  | 55.7   | 17.42 | 62.5      | 34.72 | 59.7         | 15.05 |
| 165  | INFUSION  | 80.3   | 27.86 | 63.5      | 23.35 | 67.0         | 18.41 |
| 180  | INFUSION  | 69.7   | 21.81 | 54.3      | 26.34 | 62.0         | 13.08 |

HVP = Pyrilamine maleate infusion

## Volume of Duodenal Contents

(ml/15minutes)

Balloon

| TIME<br>min | TREATMENT | SALINE |       | HISTAMINE |       | PENTAGASTRIN |       |
|-------------|-----------|--------|-------|-----------|-------|--------------|-------|
|             |           | Mean   | SEM   | Mean      | SEM   | Mean         | SEM   |
| 15          | BASAL     | 250.5  | 78.73 | 149.8     | 41.80 | 201.3        | 45.57 |
| 30          | BASAL     | 244.7  | 54.52 | 178.0     | 63.34 | 245.7        | 37.12 |
| 45          | BASAL     | 225.5  | 51.44 | 186.8     | 57.22 | 222.5        | 33.31 |
| 60          | HVP       | 215.2  | 53.61 | 190.8     | 55.71 | 212.0        | 32.13 |
| 75          |           | 183.2  | 57.45 | 228.2     | 40.55 | 170.0        | 24.97 |
| 90          |           | 222.8  | 48.59 | 299.7     | 53.26 | 183.5        | 45.25 |
| 105         | INFUSION  | 209.0  | 51.34 | 276.2     | 71.59 | 559.2        | 104.8 |
| 120         | INFUSION  | 232.5  | 53.69 | 218.7     | 72.12 | 527.0        | 108.1 |
| 135         | INFUSION  | 219.0  | 56.42 | 186.0     | 41.84 | 404.0        | 101.7 |
| 150         | INFUSION  | 177.5  | 44.21 | 197.3     | 39.75 | 503.3        | 84.9  |
| 165         | INFUSION  | 204.5  | 41.48 | 166.7     | 18.67 | 392.0        | 117.6 |
| 180         | INFUSION  | 157.5  | 58.14 | 144.5     | 14.20 | 426.0        | 105.4 |

HVP = Pyrilamine maleate infusion

## pH of Duodenal Contents

No Balloon

| TIME<br>min | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|-------------|-----------|--------|------|-----------|------|--------------|------|
|             |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15          | BASAL     | 8.22   | 0.14 | 8.05      | 0.21 | 8.53         | 0.13 |
| 30          | BASAL     | 8.14   | 0.15 | 8.00      | 0.16 | 8.62         | 0.04 |
| 45          | BASAL     | 8.13   | 0.17 | 7.96      | 0.21 | 8.52         | 0.05 |
| 60          | HVP       | 8.10   | 0.16 | 8.05      | 0.12 | 8.46         | 0.14 |
| 75          |           | 8.06   | 0.13 | 7.84      | 0.10 | 8.47         | 0.09 |
| 90          |           | 8.10   | 0.13 | 7.90      | 0.11 | 8.46         | 0.15 |
| 105         | INFUSION  | 8.12   | 0.13 | 7.97      | 0.12 | 8.42         | 0.10 |
| 120         | INFUSION  | 8.11   | 0.18 | 7.90      | 0.11 | 8.37         | 0.13 |
| 135         | INFUSION  | 8.14   | 0.09 | 7.98      | 0.15 | 8.41         | 0.10 |
| 150         | INFUSION  | 8.18   | 0.14 | 7.92      | 0.15 | 8.37         | 0.12 |
| 165         | INFUSION  | 8.04   | 0.10 | 7.98      | 0.15 | 8.38         | 0.10 |
| 180         | INFUSION  | 8.04   | 0.10 | 7.90      | 0.17 | 8.36         | 0.12 |

HVP = Pyrilamine maleate infusion

## pH of Duodenal Contents

Balloon

| TIME | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|------|-----------|--------|------|-----------|------|--------------|------|
|      |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15   | BASAL     | 8.24   | 0.09 | 8.25      | 0.05 | 8.30         | 0.14 |
| 30   | BASAL     | 8.17   | 0.12 | 8.17      | 0.12 | 8.25         | 0.14 |
| 45   | BASAL     | 8.20   | 0.11 | 8.17      | 0.14 | 8.21         | 0.12 |
| 60   | HVP       | 8.16   | 0.12 | 8.15      | 0.15 | 8.20         | 0.12 |
| 75   |           | 8.04   | 0.13 | 8.04      | 0.11 | 8.18         | 0.11 |
| 90   |           | 8.13   | 0.13 | 8.02      | 0.12 | 8.09         | 0.13 |
| 105  | INFUSION  | 8.06   | 0.11 | 8.07      | 0.16 | 8.36         | 0.05 |
| 120  | INFUSION  | 8.06   | 0.12 | 8.09      | 0.15 | 8.33         | 0.05 |
| 135  | INFUSION  | 8.03   | 0.10 | 8.05      | 0.10 | 8.26         | 0.07 |
| 150  | INFUSION  | 8.08   | 0.12 | 7.97      | 0.09 | 8.20         | 0.11 |
| 165  | INFUSION  | 8.03   | 0.10 | 7.91      | 0.09 | 8.24         | 0.03 |
| 180  | INFUSION  | 8.07   | 0.11 | 7.93      | 0.10 | 8.18         | 0.07 |

HVP = Pyrilamine maleate infusion

## Bicarbonate Concentration in Duodenal Contents

(mEq/L)

No Balloon

| TIME<br>min | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|-------------|-----------|--------|------|-----------|------|--------------|------|
|             |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15          | BASAL     | 27.70  | 2.05 | 25.39     | 3.08 | 23.23        | 2.92 |
| 30          | BASAL     | 24.21  | 3.24 | 22.94     | 2.58 | 24.06        | 2.39 |
| 45          | BASAL     | 22.36  | 2.92 | 22.36     | 1.98 | 23.11        | 2.25 |
| 60          | HVP       | 22.12  | 3.53 | 23.37     | 1.81 | 24.95        | 2.03 |
| 75          |           | 24.04  | 3.17 | 22.48     | 1.46 | 21.69        | 1.52 |
| 90          |           | 23.89  | 2.52 | 22.51     | 1.74 | 24.11        | 2.02 |
| 105         | INFUSION  | 23.61  | 2.24 | 25.01     | 2.15 | 29.28        | 2.67 |
| 120         | INFUSION  | 23.08  | 3.65 | 25.36     | 2.53 | 34.28        | 1.67 |
| 135         | INFUSION  | 23.59  | 4.28 | 24.38     | 1.72 | 35.17        | 2.21 |
| 150         | INFUSION  | 23.95  | 2.48 | 22.68     | 3.36 | 33.26        | 1.48 |
| 165         | INFUSION  | 24.48  | 2.64 | 23.88     | 1.87 | 31.82        | 2.32 |
| 180         | INFUSION  | 22.81  | 2.69 | 21.86     | 2.68 | 34.23        | 2.36 |

HVP = Pyrilamine maleate infusion

## Bicarbonate Concentration in Duodenal Contents

(mEq/L)

Balloon

| TIME<br>min | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|-------------|-----------|--------|------|-----------|------|--------------|------|
|             |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15          | BASAL     | 31.82  | 2.73 | 24.05     | 3.30 | 25.44        | 1.90 |
| 30          | BASAL     | 29.28  | 2.81 | 28.63     | 2.62 | 28.82        | 2.92 |
| 45          | BASAL     | 28.40  | 2.65 | 28.02     | 2.05 | 27.70        | 2.90 |
| 60          | HVP       | 26.29  | 3.20 | 29.52     | 1.61 | 26.38        | 2.87 |
| 75          |           | 30.95  | 3.74 | 31.44     | 0.73 | 27.34        | 2.72 |
| 90          |           | 26.71  | 4.09 | 31.55     | 1.04 | 23.97        | 3.83 |
| 105         | INFUSION  | 25.97  | 5.05 | 33.59     | 1.42 | 36.56        | 1.43 |
| 120         | INFUSION  | 27.40  | 3.77 | 32.42     | 2.90 | 36.04        | 2.55 |
| 135         | INFUSION  | 28.02  | 2.12 | 29.70     | 2.19 | 36.51        | 2.85 |
| 150         | INFUSION  | 27.36  | 3.76 | 28.71     | 1.67 | 36.77        | 2.68 |
| 165         | INFUSION  | 30.91  | 5.98 | 28.81     | 1.66 | 37.08        | 2.41 |
| 180         | INFUSION  | 26.03  | 3.34 | 27.83     | 2.18 | 37.13        | 1.87 |

HVP = Pyrilamine maleate infusion

## Sodium Concentration in Duodenal Contents

(mEq/L)

No Balloon

| TIME<br>min | TREATMENT | SALINE |       | HISTAMINE |      | PENTAGASTRIN |       |
|-------------|-----------|--------|-------|-----------|------|--------------|-------|
|             |           | Mean   | SEM   | Mean      | SEM  | Mean         | SEM   |
| 15          | BASAL     | 155.2  | 4.86  | 143.2     | 2.59 | 144.2        | 1.95  |
| 30          | BASAL     | 154.2  | 5.54  | 142.3     | 1.90 | 145.4        | 2.48  |
| 45          | BASAL     | 157.2  | 8.78  | 141.7     | 2.28 | 144.2        | 2.56  |
| 60          | HVP       | 153.6  | 5.05  | 142.2     | 1.99 | 139.2        | 4.54  |
| 75          |           | 151.9  | 4.72  | 142.2     | 2.62 | 153.4        | 10.80 |
| 90          |           | 160.9  | 11.02 | 143.2     | 1.18 | 157.2        | 10.15 |
| 105         | INFUSION  | 151.1  | 6.99  | 141.6     | 0.87 | 143.0        | 1.87  |
| 120         | INFUSION  | 162.4  | 11.23 | 139.7     | 1.48 | 142.1        | 2.20  |
| 135         | INFUSION  | 152.0  | 9.44  | 135.8     | 3.82 | 142.4        | 2.82  |
| 150         | INFUSION  | 149.3  | 8.52  | 138.3     | 1.70 | 144.4        | 3.73  |
| 165         | INFUSION  | 151.5  | 5.31  | 135.7     | 2.26 | 143.7        | 1.88  |
| 180         | INFUSION  | 146.4  | 5.82  | 134.4     | 3.78 | 146.2        | 2.95  |

HVP = Pyrilamine maleate infusion

## Sodium Concentration in Duodenal Contents

(mEq/L)

Balloon

| TIME<br>min | TREATMENT | SALINE |       | HISTAMINE |      | PENTAGASTRIN |       |
|-------------|-----------|--------|-------|-----------|------|--------------|-------|
|             |           | Mean   | SEM   | Mean      | SEM  | Mean         | SEM   |
| 15          | BASAL     | 138.6  | 8.41  | 145.0     | 4.39 | 133.8        | 7.76  |
| 30          | BASAL     | 138.2  | 6.98  | 136.4     | 5.29 | 136.9        | 5.98  |
| 45          | BASAL     | 132.4  | 11.75 | 134.9     | 4.39 | 141.6        | 6.43  |
| 60          | HVP       | 140.3  | 9.75  | 131.6     | 6.30 | 137.1        | 4.55  |
| 75          |           | 134.0  | 9.88  | 135.2     | 6.85 | 140.0        | 6.47  |
| 90          |           | 132.1  | 6.65  | 141.5     | 3.91 | 136.0        | 5.97  |
| 105         | INFUSION  | 136.9  | 5.55  | 137.1     | 4.63 | 142.0        | 5.56  |
| 120         | INFUSION  | 133.7  | 9.76  | 139.8     | 4.94 | 140.4        | 9.43  |
| 135         | INFUSION  | 130.9  | 12.34 | 137.0     | 4.20 | 142.2        | 7.90  |
| 150         | INFUSION  | 141.0  | 6.83  | 141.5     | 2.20 | 142.2        | 7.15  |
| 165         | INFUSION  | 141.3  | 7.44  | 143.7     | 2.42 | 143.0        | 7.71  |
| 180         | INFUSION  | 134.8  | 6.67  | 142.5     | 1.92 | 143.8        | 11.14 |

HVP = Pyrilamine maleate infusion

## Potassium Concentration in Duodenal Contents

(mEq/L)

No Balloon

| TIME<br>min | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|-------------|-----------|--------|------|-----------|------|--------------|------|
|             |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15          | BASAL     | 4.62   | 0.28 | 4.40      | 0.09 | 4.47         | 0.08 |
| 30          | BASAL     | 4.69   | 0.30 | 4.29      | 0.07 | 4.45         | 0.06 |
| 45          | BASAL     | 4.88   | 0.36 | 4.22      | 0.17 | 4.39         | 0.09 |
| 60          | HVP       | 4.68   | 0.29 | 4.23      | 0.14 | 4.31         | 0.11 |
| 75          |           | 4.45   | 0.28 | 4.12      | 0.13 | 4.68         | 0.42 |
| 90          |           | 4.43   | 0.25 | 4.13      | 0.09 | 4.66         | 0.37 |
| 105         | INFUSION  | 4.57   | 0.34 | 3.97      | 0.09 | 4.01         | 0.14 |
| 120         | INFUSION  | 4.75   | 0.45 | 3.86      | 0.09 | 3.82         | 0.09 |
| 135         | INFUSION  | 4.34   | 0.31 | 3.88      | 0.15 | 3.70         | 0.09 |
| 150         | INFUSION  | 4.53   | 0.37 | 3.80      | 0.10 | 3.78         | 0.16 |
| 165         | INFUSION  | 4.15   | 0.26 | 3.91      | 0.22 | 3.65         | 0.09 |
| 180         | INFUSION  | 4.37   | 0.28 | 3.90      | 0.18 | 3.63         | 0.12 |

HVP = Pyrilamine maleate infusion

## Potassium Concentration in Duodenal Contents

(mEq/L)

Balloon

| TIME | TREATMENT | SALINE |      | HISTAMINE |      | PENTAGASTRIN |      |
|------|-----------|--------|------|-----------|------|--------------|------|
| min  |           | Mean   | SEM  | Mean      | SEM  | Mean         | SEM  |
| 15   | BASAL     | 3.86   | 0.29 | 4.17      | 0.15 | 3.96         | 0.29 |
| 30   | BASAL     | 3.87   | 0.28 | 3.94      | 0.14 | 3.91         | 0.23 |
| 45   | BASAL     | 3.72   | 0.39 | 3.83      | 0.11 | 4.14         | 0.30 |
| 60   | HVP       | 3.95   | 0.37 | 3.79      | 0.18 | 3.88         | 0.20 |
| 75   |           | 3.71   | 0.36 | 3.82      | 0.18 | 3.95         | 0.24 |
| 90   |           | 3.68   | 0.30 | 3.96      | 0.07 | 3.95         | 0.29 |
| 105  | INFUSION  | 4.19   | 0.50 | 3.85      | 0.12 | 3.77         | 0.18 |
| 120  | INFUSION  | 3.58   | 0.35 | 3.78      | 0.06 | 3.50         | 0.28 |
| 135  | INFUSION  | 3.66   | 0.44 | 3.67      | 0.12 | 3.73         | 0.34 |
| 150  | INFUSION  | 3.87   | 0.28 | 3.63      | 0.10 | 3.62         | 0.34 |
| 165  | INFUSION  | 3.83   | 0.30 | 3.71      | 0.11 | 3.57         | 0.31 |
| 180  | INFUSION  | 3.61   | 0.28 | 3.68      | 0.12 | 3.49         | 0.39 |

HVP = Pyrilamine maleate infusion

## Chloride Concentration in Duodenal Contents

(mEq/L)

No Balloon

| TIME | TREATMENT | SALINE |      | HISTAMINE |       | PENTAGASTRIN |      |
|------|-----------|--------|------|-----------|-------|--------------|------|
|      |           | Mean   | SEM  | Mean      | SEM   | Mean         | SEM  |
| 15   | BASAL     | 119.5  | 3.17 | 102.9     | 6.68  | 118.2        | 4.80 |
| 30   | BASAL     | 123.4  | 3.98 | 102.7     | 4.00  | 126.6        | 6.12 |
| 45   | BASAL     | 124.6  | 4.09 | 101.8     | 5.92  | 129.4        | 8.91 |
| 60   | HVP       | 124.8  | 4.01 | 105.8     | 4.99  | 110.1        | 6.69 |
| 75   |           | 123.5  | 4.73 | 107.3     | 3.45  | 128.6        | 4.58 |
| 90   |           | 121.3  | 7.03 | 112.6     | 6.77  | 124.7        | 4.78 |
| 105  | INFUSION  | 126.5  | 6.94 | 116.5     | 5.52  | 119.7        | 7.13 |
| 120  | INFUSION  | 136.3  | 3.41 | 110.5     | 4.70  | 113.4        | 5.09 |
| 135  | INFUSION  | 137.1  | 6.40 | 108.1     | 6.70  | 112.4        | 4.49 |
| 150  | INFUSION  | 126.2  | 8.96 | 102.7     | 10.25 | 105.4        | 7.85 |
| 165  | INFUSION  | 136.1  | 5.70 | 105.7     | 7.32  | 117.8        | 7.41 |
| 180  | INFUSION  | 135.1  | 5.39 | 100.9     | 6.67  | 112.4        | 4.72 |

HVP = Pyrilamine maleate infusion

## Chloride Concentration in Duodenal Contents

(mEq/L)

Balloon

| TIME<br>min | TREATMENT | SALINE |      | HISTAMINE |       | PENTAGASTRIN |      |
|-------------|-----------|--------|------|-----------|-------|--------------|------|
|             |           | Mean   | SEM  | Mean      | SEM   | Mean         | SEM  |
| 15          | BASAL     | 126.2  | 4.91 | 126.2     | 7.55  | 122.7        | 6.69 |
| 30          | BASAL     | 125.4  | 4.45 | 128.0     | 8.08  | 128.1        | 5.93 |
| 45          | BASAL     | 122.4  | 7.44 | 125.1     | 11.79 | 130.8        | 4.88 |
| 60          | HVP       | 116.9  | 7.71 | 126.8     | 9.98  | 127.0        | 5.13 |
| 75          |           | 120.9  | 3.78 | 122.7     | 3.81  | 131.4        | 5.14 |
| 90          |           | 117.3  | 2.65 | 121.9     | 4.09  | 129.1        | 7.06 |
| 105         | INFUSION  | 122.0  | 3.03 | 118.0     | 4.37  | 110.0        | 3.65 |
| 120         | INFUSION  | 123.6  | 5.12 | 121.1     | 4.00  | 104.1        | 5.39 |
| 135         | INFUSION  | 126.0  | 5.19 | 110.3     | 4.05  | 110.0        | 1.95 |
| 150         | INFUSION  | 129.6  | 5.13 | 115.4     | 3.75  | 108.7        | 3.82 |
| 165         | INFUSION  | 128.6  | 5.72 | 111.8     | 3.33  | 110.1        | 2.67 |
| 180         | INFUSION  | 129.9  | 6.85 | 113.2     | 2.03  | 106.9        | 2.70 |

HVP = Pyrilamine maleate infusion

## APPENDIX D

### STATISTICAL ANALYSIS OF HISTAMINE DOSE RESPONSE DATA

Analysis by General Linear Model with One Way ANOVA for repeated measures using SigmaStat software.

#### Gastric Content Volume

| Source   | DF | SS        | MS       | F Value     | P Value     |
|----------|----|-----------|----------|-------------|-------------|
| HORSES   | 5  | 1037113.3 | 207422.7 | 0.00000250  |             |
| DOSE     | 4  | 1121695.0 | 280423.7 | 23.46696808 | 0.000000618 |
| Residual | 18 | 215095.0  | 11949.7  |             |             |
| Total    | 27 | 2313867.9 | 85698.8  |             |             |

#### Acid Concentration of Gastric Contents

| Source   | DF | SS      | MS      | F Value   | P Value      |
|----------|----|---------|---------|-----------|--------------|
| HORSES   | 5  | 12717.1 | 2543.4  | 0.000791  |              |
| DOSE     | 4  | 51314.1 | 12828.5 | 35.833490 | 0.0000000241 |
| Residual | 18 | 6444.1  | 358.0   |           |              |
| Total    | 27 | 69398.9 | 2570.3  |           |              |

Acid Output of Gastric Contents

| Source   | DF | SS      | MS       | F Value       | P Value      |
|----------|----|---------|----------|---------------|--------------|
| HORSES   | 5  | 0.04418 | 0.008836 | 0.00000000214 |              |
| DOSE     | 4  | 0.11481 | 0.028703 | 0.0140        | 0.0000000000 |
| Residual | 18 | 0.00369 | 0.000205 |               |              |
| Total    | 27 | 0.15768 | 0.005840 |               |              |

Sodium Concentration of Gastric Contents

| Source   | DF | SS      | MS     | F Value      | P Value   |
|----------|----|---------|--------|--------------|-----------|
| HORSES   | 5  | 46911.3 | 9382.3 | 0.000000902  |           |
| DOSE     | 4  | 27197.0 | 6799.2 | 14.454750403 | 0.0000188 |
| Residual | 18 | 8466.9  | 470.4  |              |           |
| Total    | 27 | 84638.5 | 3134.8 |              |           |

Sodium Output of Gastric Contents

| Source   | DF | SS      | MS       | F Value    | P Value |
|----------|----|---------|----------|------------|---------|
| HORSES   | 5  | 0.08123 | 0.016245 | 0.00000932 |         |
| DOSE     | 4  | 0.00187 | 0.000468 | 0.41486401 | 0.796   |
| Residual | 18 | 0.02029 | 0.001127 |            |         |
| Total    | 27 | 0.10473 | 0.003879 |            |         |

APPENDIX E  
STATISTICAL ANALYSIS OF PYRILAMINE MALEATE DATA

Analysis performed using SigmaStat software by General  
Linear Model as Paired t-test.

Basal Collections

| Parameter          | t       | DF | P Value |
|--------------------|---------|----|---------|
| Volume             | 0.284   | 7  | 0.7849  |
| Acid Concentration | -0.0792 | 7  | 0.9391  |
| Acid Output        | -0.189  | 7  | 0.8553  |

Post-pyrilamine Collections

| Parameter          | t    | DF | P Value |
|--------------------|------|----|---------|
| Volume             | 3.23 | 7  | 0.0145  |
| Acid Concentration | 2.06 | 7  | 0.0785  |
| Acid Output        | 5.61 | 7  | 0.0008  |

Early Infusion Collections

| Parameter          | t      | DF | P Value |
|--------------------|--------|----|---------|
| Volume             | 1.38   | 11 | 0.1953  |
| Acid Concentration | -0.740 | 11 | 0.4747  |
| Acid Output        | 2.54   | 11 | 0.0274  |

Late Infusion Collections

| Parameter          | t      | DF | P Value |
|--------------------|--------|----|---------|
| Volume             | 0.523  | 11 | 0.6113  |
| Acid Concentration | -0.913 | 11 | 0.3807  |
| Acid Output        | 3.77   | 11 | 0.0031  |

APPENDIX F  
STATISTICAL ANALYSIS OF CATHETER/NO CATHETER DATA

Analysis is by General Linear Model with Two Way ANOVA  
using SigmaStat software.

Gastric Content Volume

| Source    | DF | SS          | MS          | F Value | P Value |
|-----------|----|-------------|-------------|---------|---------|
| CATHETER  | 1  | 1310221.008 | 1310221.008 | 41.444  | <0.001  |
| TIME      | 3  | 2035066.025 | 678355.342  | 21.457  | <0.001  |
| CATH*TIME | 3  | 22197.025   | 7399.008    | 0.234   | 0.872   |
| Residual  | 72 | 2276250.917 | 31614.596   |         |         |
| Total     | 79 | 5812169.487 | 73571.766   |         |         |

Acid Concentration of Gastric Content

| Source    | DF | SS        | MS       | F Value | P Value |
|-----------|----|-----------|----------|---------|---------|
| CATHETER  | 1  | 1722.366  | 1722.366 | 6.093   | 0.016   |
| TIME      | 3  | 4863.528  | 1621.176 | 5.735   | 0.001   |
| CATH*TIME | 3  | 253.190   | 84.397   | 0.299   | 0.826   |
| Residual  | 72 | 20353.253 | 282.684  |         |         |
| Total     | 79 | 27373.608 | 346.501  |         |         |

Acid Output of Gastric Content

| Source    | DF | SS        | MS       | F Value | P Value |
|-----------|----|-----------|----------|---------|---------|
| CATHETER  | 1  | 3099.751  | 3099.751 | 10.970  | 0.001   |
| TIME      | 3  | 29506.653 | 9835.551 | 34.808  | <0.001  |
| CATH*TIME | 3  | 741.643   | 247.214  | 0.875   | 0.458   |
| Residual  | 72 | 20344.690 | 282.565  |         |         |
| Total     | 79 | 56625.792 | 716.782  |         |         |

Sodium Concentration of Gastric Content

| Source    | DF | SS        | MS       | F Value | P Value |
|-----------|----|-----------|----------|---------|---------|
| CATHETER  | 1  | 194.948   | 194.948  | 0.612   | 0.437   |
| TIME      | 3  | 3880.260  | 1293.420 | 4.059   | 0.010   |
| CATH*TIME | 3  | 203.853   | 67.951   | 0.213   | 0.887   |
| Residual  | 72 | 22941.946 | 318.638  |         |         |
| Total     | 79 | 27518.836 | 348.340  |         |         |

Sodium Output of Gastric Content

| Source    | DF | SS         | MS        | F Value | P Value |
|-----------|----|------------|-----------|---------|---------|
| CATHETER  | 1  | 32851.071  | 32851.071 | 11.703  | 0.001   |
| TIME      | 3  | 76666.512  | 25555.504 | 9.104   | <0.001  |
| CATH*TIME | 3  | 649.446    | 216.482   | 0.0771  | 0.972   |
| Residual  | 72 | 202115.891 | 2807.165  |         |         |
| Total     | 79 | 313360.908 | 3966.594  |         |         |

APPENDIX G  
STATISTICAL ANALYSIS OF BALLOON/NO BALLOON DATA

The SAS System

General Linear Models Procedure

| Class   | Levels | Values                                       |
|---------|--------|----------------------------------------------|
| HORSE   | 6      | B D E H I T                                  |
| BALLOON | 2      | no yes                                       |
| DRUG    | 3      | histamine pentagastrin<br>saline             |
| TIME    | 12     | 15 30 45 60 75 90 105 120<br>135 150 165 180 |

Abbreviations for following ANOVA tables:

B or b = Balloon vs. No Balloon

t = time

d = drug

\* = interaction

pre = prior to infusion (t=15-90 minutes)

post = during infusion (t=105-180 minutes)

Gastric Content Volume

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 1581979.484 | 316395.897  | 43.98   | 0.0001 |
| BALLOON(B)   | 1  | 6964934.280 | 6964934.280 | 968.07  | 0.0001 |
| DRUG         | 2  | 1965459.060 | 982729.530  | 136.59  | 0.0001 |
| B*DRUG       | 2  | 217416.144  | 108708.072  | 15.11   | 0.0001 |
| HORSE*B*DRUG | 25 | 1233421.502 | 49336.860   | 6.86    | 0.0001 |
| TIME         | 11 | 4288302.581 | 389845.689  | 54.19   | 0.0001 |
| B*TIME       | 11 | 237064.414  | 21551.310   | 3.00    | 0.0008 |
| DRUG*TIME    | 22 | 1533188.995 | 69690.409   | 9.69    | 0.0001 |
| B*DRUG*TIME  | 22 | 86068.579   | 3912.208    | 0.54    | 0.9552 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 518680.912  | 103736.182  | 14.42   | 0.0001 |
| post,t effect | 5  | 1103288.981 | 220657.796  | 30.67   | 0.0001 |
| pre, b*t      | 5  | 13559.245   | 2711.849    | 0.38    | 0.8644 |
| post,b*t      | 5  | 96643.111   | 19328.622   | 2.69    | 0.0214 |
| pre,drug*t    | 10 | 31124.463   | 3112.446    | 0.43    | 0.9302 |
| post,drug*t   | 10 | 368044.491  | 36804.449   | 5.12    | 0.0001 |
| pre, b*drug*t | 10 | 26594.907   | 2659.491    | 0.37    | 0.9591 |
| post,b*drug*t | 10 | 34653.361   | 3465.336    | 0.48    | 0.9016 |

| Source        | DF | SS_N       | MS_N       | F Value | PValue  |
|---------------|----|------------|------------|---------|---------|
| pre, b effect | 1  | 2605905.67 | 2605905.67 | 92.193  | 0.00000 |
| post,b effect | 1  | 4485890.67 | 4485890.67 | 158.704 | 0.00000 |
| pre, d effect | 2  | 60907.37   | 30453.69   | 1.077   | 0.35223 |
| post,d effect | 2  | 3038571.73 | 1519285.87 | 53.750  | 0.00000 |
| pre, d*b      | 2  | 48270.26   | 24135.13   | 0.854   | 0.43502 |
| post, d*b     | 2  | 193966.19  | 96983.10   | 3.431   | 0.04437 |

Gastric Content pH

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 193.5264900 | 38.7052980  | 34.44   | 0.0001 |
| BALLOON(B)   | 1  | 2.9320558   | 2.9320558   | 2.61    | 0.1072 |
| DRUG         | 2  | 19.7845588  | 9.8922794   | 8.80    | 0.0002 |
| B*DRUG       | 2  | 13.0219616  | 6.5109808   | 5.79    | 0.0034 |
| HORSE*B*DRUG | 25 | 290.8255252 | 11.6330210  | 10.35   | 0.0001 |
| TIME         | 11 | 40.6180692  | 3.6925517   | 3.29    | 0.0003 |
| B*TIME       | 11 | 11.5292525  | 1.0481139   | 0.93    | 0.5091 |
| DRUG*TIME    | 22 | 53.9146301  | 2.4506650   | 2.18    | 0.0019 |
| B*DRUG*TIME  | 22 | 28.2382718  | 1.2835578   | 1.14    | 0.3000 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 12.86303704 | 2.57260741  | 2.29    | 0.0457 |
| post,t effect | 5  | 12.51123009 | 2.50224602  | 2.23    | 0.0514 |
| pre, b*t      | 5  | 5.23759259  | 1.04751852  | 0.93    | 0.4603 |
| post,b*t      | 5  | 3.09004861  | 0.61800972  | 0.55    | 0.7384 |
| pre,drug*t    | 10 | 14.60956574 | 1.46095657  | 1.30    | 0.2292 |
| post,drug*t   | 10 | 3.51883696  | 0.35188380  | 0.31    | 0.9776 |
| pre, b*drug*t | 10 | 5.42322130  | 0.54232213  | 0.48    | 0.9011 |
| post,b*drug*t | 10 | 5.79351944  | 0.57935194  | 0.52    | 0.8791 |

| Source        | DF | SS_N    | MS_N    | F Value | PValue  |
|---------------|----|---------|---------|---------|---------|
| pre, b effect | 1  | 0.0030  | 0.0030  | 0.00046 | 0.98295 |
| post,b effect | 1  | 6.1307  | 6.1307  | 0.96115 | 0.33473 |
| pre, d effect | 2  | 2.8688  | 1.4344  | 0.22488 | 0.79995 |
| post,d effect | 2  | 52.7020 | 26.3510 | 4.13123 | 0.02600 |
| pre, d*b      | 2  | 22.7303 | 11.3651 | 1.78179 | 0.18567 |
| post, d*b     | 2  | 7.3132  | 3.6566  | 0.57327 | 0.56972 |

Acid Concentration in Gastric Contents

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 32666.61465 | 6533.32293  | 39.13   | 0.0001 |
| BALLOON(B)   | 1  | 31688.10187 | 31688.10187 | 189.81  | 0.0001 |
| DRUG         | 2  | 34270.57097 | 17135.28549 | 102.64  | 0.0001 |
| B*DRUG       | 2  | 12733.08847 | 6366.54424  | 38.14   | 0.0001 |
| HORSE*B*DRUG | 25 | 39094.01299 | 1563.76052  | 9.37    | 0.0001 |
| TIME         | 11 | 67444.90174 | 6131.35470  | 36.73   | 0.0001 |
| B*TIME       | 11 | 7895.62062  | 717.78369   | 4.3     | 0.0001 |
| DRUG*TIME    | 22 | 65110.70292 | 2959.57741  | 17.73   | 0.0001 |
| B*DRUG*TIME  | 22 | 3948.51653  | 179.47802   | 1.08    | 0.3725 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 5915.33764  | 1183.06753  | 7.09    | 0.0001 |
| post,t effect | 5  | 25597.12889 | 5119.42578  | 30.67   | 0.0001 |
| pre, b*t      | 5  | 662.13023   | 132.42605   | 0.79    | 0.5551 |
| post,b*t      | 5  | 1371.83370  | 274.36674   | 1.64    | 0.1480 |
| pre,drug*t    | 10 | 1742.00250  | 174.20025   | 1.04    | 0.4064 |
| post,drug*t   | 10 | 9913.47028  | 991.34703   | 5.94    | 0.0001 |
| pre, b*drug*t | 10 | 495.34380   | 49.53438    | 0.30    | 0.9817 |
| post,b*drug*t | 10 | 664.93880   | 66.49388    | 0.40    | 0.9470 |

| Source        | DF | SS_N     | MS_N     | F Value | PValue  |
|---------------|----|----------|----------|---------|---------|
| pre, b effect | 1  | 5146.06  | 5146.06  | 5.9468  | 0.02075 |
| post,b effect | 1  | 32403.70 | 32404.70 | 37.4457 | 0.00000 |
| pre, d effect | 2  | 1264.93  | 632.46   | 0.7309  | 0.48971 |
| post,d effect | 2  | 86460.88 | 43230.44 | 49.9571 | 0.00000 |
| pre, d*b      | 2  | 3510.22  | 1755.11  | 2.0282  | 0.14889 |
| post, d*b     | 2  | 12011.10 | 6005.55  | 6.9400  | 0.00327 |

Acid Output in Gastric Contents

| Source       | DF | Type I SS  | Mean Square | F Value | Pr > F |
|--------------|----|------------|-------------|---------|--------|
| HORSE        | 5  | 0.08082750 | 0.01616550  | 106.35  | 0.0001 |
| BALLOON (B)  | 1  | 0.00388800 | 0.00388800  | 25.58   | 0.0001 |
| DRUG         | 2  | 0.06885906 | 0.03442953  | 226.50  | 0.0001 |
| B*DRUG       | 2  | 0.00859756 | 0.00429878  | 28.28   | 0.0001 |
| HORSE*B*DRUG | 25 | 0.03029697 | 0.00121188  | 7.97    | 0.0001 |
| TIME         | 11 | 0.16610719 | 0.01510065  | 99.34   | 0.0001 |
| B*TIME       | 11 | 0.00125706 | 0.00011428  | 0.75    | 0.6881 |
| DRUG*TIME    | 22 | 0.09332317 | 0.00424196  | 27.91   | 0.0001 |
| B*DRUG*TIME  | 22 | 0.00770722 | 0.00035033  | 2.30    | 0.0009 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 0.01059159  | 0.00211832  | 13.94   | 0.0001 |
| post,t effect | 5  | 0.06323181  | 0.01264636  | 83.20   | 0.0001 |
| pre, b*t      | 5  | 0.00036315  | 0.00007263  | 0.48    | 0.7928 |
| post,b*t      | 5  | 0.00029654  | 0.00005931  | 0.39    | 0.8555 |
| pre,drug*t    | 10 | 0.00091566  | 0.00009157  | 0.60    | 0.8118 |
| post,drug*t   | 10 | 0.02217682  | 0.00221768  | 14.59   | 0.0001 |
| pre, b*drug*t | 10 | 0.00078794  | 0.00007879  | 0.52    | 0.8770 |
| post,b*drug*t | 10 | 0.00209071  | 0.00020907  | 1.38    | 0.1902 |

| Source        | DF | SS_N    | MS_N     | F Value | PValue  |
|---------------|----|---------|----------|---------|---------|
| pre, b effect | 1  | 0.00377 | 0.003767 | 5.523   | 0.02517 |
| post,b effect | 1  | 0.00072 | 0.000719 | 1.054   | 0.31240 |
| pre, d effect | 2  | 0.00000 | 0.000002 | 0.003   | 0.99654 |
| post,d effect | 2  | 0.13909 | 0.069543 | 101.977 | 0.00000 |
| pre, d*b      | 2  | 0.00028 | 0.000142 | 0.208   | 0.81358 |
| post, d*b     | 2  | 0.01314 | 0.006571 | 9.636   | 0.00054 |

Sodium Concentration in Gastric Contents

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 30181.87067 | 6036.37413  | 38.97   | 0.0001 |
| BALLOON(B)   | 1  | 24969.04280 | 24969.04280 | 161.21  | 0.0001 |
| DRUG         | 2  | 44132.80588 | 22066.40294 | 142.47  | 0.0001 |
| B*DRUG       | 2  | 8922.09532  | 4461.04766  | 28.80   | 0.0001 |
| HORSE*B*DRUG | 25 | 46055.64502 | 1842.22580  | 11.89   | 0.0001 |
| TIME         | 11 | 73160.32748 | 6650.93886  | 42.94   | 0.0001 |
| B*TIME       | 11 | 7086.57970  | 644.23452   | 4.16    | 0.0001 |
| DRUG*TIME    | 22 | 56593.70301 | 2572.44105  | 16.61   | 0.0001 |
| B*DRUG*TIME  | 22 | 4775.21468  | 217.05521   | 1.40    | 0.1101 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 4954.00037  | 990.80007   | 6.40    | 0.0001 |
| post,t effect | 5  | 24135.98708 | 4827.19742  | 31.17   | 0.0001 |
| pre, b*t      | 5  | 437.04981   | 87.40996    | 0.56    | 0.7273 |
| post,b*t      | 5  | 1472.39968  | 294.47994   | 1.90    | 0.0936 |
| pre,drug*t    | 10 | 1511.62991  | 151.16299   | 0.98    | 0.4641 |
| post,drug*t   | 10 | 9416.88083  | 941.68808   | 6.08    | 0.0001 |
| pre, b*drug*t | 10 | 494.41269   | 49.44127    | 0.32    | 0.9759 |
| post,b*drug*t | 10 | 1359.65435  | 135.96544   | 0.88    | 0.5542 |

| Source        | DF | SS_N     | MS_N     | F Value | PValue  |
|---------------|----|----------|----------|---------|---------|
| pre, b effect | 1  | 3703.48  | 3703.48  | 3.7088  | 0.06386 |
| post,b effect | 1  | 26442.69 | 26442.69 | 26.4810 | 0.00002 |
| pre, d effect | 2  | 250.42   | 125.21   | 0.1254  | 0.88262 |
| post,d effect | 2  | 89547.58 | 44773.79 | 44.8386 | 0.00000 |
| pre, d*b      | 2  | 8239.65  | 4119.83  | 4.1258  | 0.02636 |
| post, d*b     | 2  | 3603.59  | 1801.79  | 1.8044  | 0.18235 |

Sodium Output in Gastric Contents

| Source       | DF | Type I SS  | Mean Square | F Value | Pr > F |
|--------------|----|------------|-------------|---------|--------|
| HORSE        | 5  | 0.02352621 | 0.00470524  | 12.97   | 0.0001 |
| BALLOON(B)   | 1  | 0.43675692 | 0.43675692  | 1204.21 | 0.0001 |
| DRUG         | 2  | 0.08437257 | 0.04218628  | 116.31  | 0.0001 |
| B*DRUG       | 2  | 0.03794764 | 0.01897382  | 52.31   | 0.0001 |
| HORSE*B*DRUG | 25 | 0.07838351 | 0.00313534  | 8.64    | 0.0001 |
| TIME         | 11 | 0.03514183 | 0.00319471  | 8.81    | 0.0001 |
| B*TIME       | 11 | 0.01913108 | 0.00173919  | 4.80    | 0.0001 |
| DRUG*TIME    | 22 | 0.05861341 | 0.00266425  | 7.35    | 0.0001 |
| B*DRUG*TIME  | 22 | 0.01446002 | 0.00065727  | 1.81    | 0.0150 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 0.01271226  | 0.00254245  | 7.01    | 0.0001 |
| post,t effect | 5  | 0.00408749  | 0.00081750  | 2.25    | 0.0488 |
| pre, b*t      | 5  | 0.0079682   | 0.00015936  | 0.44    | 0.8209 |
| post,b*t      | 5  | 0.00552939  | 0.00110588  | 3.05    | 0.0105 |
| pre,drug*t    | 10 | 0.00294658  | 0.00029466  | 0.81    | 0.6169 |
| post,drug*t   | 10 | 0.01127471  | 0.00112747  | 3.11    | 0.0008 |
| pre, b*drug*t | 10 | 0.00221936  | 0.00022194  | 0.61    | 0.8037 |
| post,b*drug*t | 10 | 0.00474130  | 0.00047413  | 1.31    | 0.2251 |

| Source        | DF | SS_N    | MS_N    | F Value | PValue  |
|---------------|----|---------|---------|---------|---------|
| pre, b effect | 1  | 0.15026 | 0.15026 | 85.967  | 0.00000 |
| post,b effect | 1  | 0.29794 | 0.29794 | 170.458 | 0.00000 |
| pre, d effect | 2  | 0.00323 | 0.00161 | 0.923   | 0.40798 |
| post,d effect | 2  | 0.12425 | 0.06213 | 35.544  | 0.00000 |
| pre, d*b      | 2  | 0.00641 | 0.00321 | 1.834   | 0.17659 |
| post, d*b     | 2  | 0.03874 | 0.01937 | 11.083  | 0.00023 |

Potassium Concentration in Gastric Contents

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 139.934838  | 27.986968   | 9.51    | 0.0001 |
| BALLOON(B)   | 1  | 209.585208  | 209.585208  | 71.22   | 0.0001 |
| DRUG         | 2  | 315.970880  | 157.985440  | 53.68   | 0.0001 |
| B*DRUG       | 2  | 169.367639  | 84.683819   | 28.78   | 0.0001 |
| HORSE*B*DRUG | 25 | 745.549468  | 29.821979   | 10.13   | 0.0001 |
| TIME         | 11 | 1413.509699 | 128.500882  | 43.66   | 0.0001 |
| B*TIME       | 11 | 195.413403  | 17.764855   | 6.04    | 0.0001 |
| DRUG*TIME    | 22 | 1009.475787 | 45.885263   | 15.59   | 0.0001 |
| B*DRUG*TIME  | 22 | 72.474583   | 3.294299    | 1.12    | 0.3235 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 229.096343  | 45.819269   | 15.57   | 0.0001 |
| post,t effect | 5  | 261.283148  | 52.256630   | 17.76   | 0.0001 |
| pre, b*t      | 5  | 6.743009    | 1.348602    | 0.46    | 0.8072 |
| post,b*t      | 5  | 20.045370   | 4.009074    | 1.36    | 0.2381 |
| pre,drug*t    | 10 | 25.108241   | 2.510824    | 0.85    | 0.5777 |
| post,drug*t   | 10 | 157.176574  | 15.717657   | 5.34    | 0.0001 |
| pre, b*drug*t | 10 | 13.242685   | 1.324269    | 0.45    | 0.9207 |
| post,b*drug*t | 10 | 24.664352   | 2.466435    | 0.84    | 0.5921 |

| Source        | DF | SS      | N | MS_N    | F Value | PValue  |
|---------------|----|---------|---|---------|---------|---------|
| pre, b effect | 1  | 1.11    |   | 1.11    | 0.0679  | 0.79620 |
| post,b effect | 1  | 377.10  |   | 377.098 | 23.0184 | 0.00004 |
| pre, d effect | 2  | 75.94   |   | 37.968  | 2.3176  | 0.11581 |
| post,d effect | 2  | 1067.23 |   | 533.613 | 32.5723 | 0.00000 |
| pre, d*b      | 2  | 32.17   |   | 16.085  | 0.9818  | 0.38628 |
| post, d*b     | 2  | 171.77  |   | 85.883  | 5.2424  | 0.01112 |

Potassium Output in Gastric Contents

| Source       | DF | Type I SS  | Mean Square | F Value | Pr > F |
|--------------|----|------------|-------------|---------|--------|
| HORSE        | 5  | 0.00124741 | 0.00024948  | 36.27   | 0.0001 |
| BALLOON(B)   | 1  | 0.00204972 | 0.00204972  | 298.00  | 0.0001 |
| DRUG         | 2  | 0.00157501 | 0.00078751  | 114.49  | 0.0001 |
| B*DRUG       | 2  | 0.00000867 | 0.00000434  | 0.63    | 0.5331 |
| HORSE*B*DRUG | 25 | 0.00099991 | 0.00004000  | 5.81    | 0.0001 |
| TIME         | 11 | 0.00552684 | 0.00050244  | 73.05   | 0.0001 |
| B*TIME       | 11 | 0.00006758 | 0.00000614  | 0.89    | 0.5473 |
| DRUG*TIME    | 22 | 0.00214371 | 0.00009744  | 14.17   | 0.0001 |
| B*DRUG*TIME  | 22 | 0.00008627 | 0.00000392  | 0.57    | 0.9417 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 0.00065783  | 0.00013157  | 19.13   | 0.0001 |
| post,t effect | 5  | 0.00148549  | 0.00029710  | 43.19   | 0.0001 |
| pre, b*t      | 5  | 0.00002122  | 0.00000424  | 0.62    | 0.6869 |
| post,b*t      | 5  | 0.00004630  | 0.00000926  | 1.35    | 0.2444 |
| pre,drug*t    | 10 | 0.00003189  | 0.00000319  | 0.46    | 0.9127 |
| post,drug*t   | 10 | 0.00050381  | 0.00005038  | 7.32    | 0.0001 |
| pre, b*drug*t | 10 | 0.00001878  | 0.00000188  | 0.27    | 0.9867 |
| post,b*drug*t | 10 | 0.00004516  | 0.00000452  | 0.66    | 0.7645 |

| Source        | DF | SS_N      | MS_N      | F Value | PValue  |
|---------------|----|-----------|-----------|---------|---------|
| pre, b effect | 1  | 0.0010140 | 0.0010140 | 43.2643 | 0.00000 |
| post,b effect | 1  | 0.0010358 | 0.0010358 | 44.1937 | 0.00000 |
| pre, d effect | 2  | 0.0000404 | 0.0000202 | 0.8628  | 0.43094 |
| post,d effect | 2  | 0.0031426 | 0.0015713 | 67.0422 | 0.00000 |
| pre, d*b      | 2  | 0.0000190 | 0.0000095 | 0.4053  | 0.66991 |
| post, d*b     | 2  | 0.0000120 | 0.0000060 | 0.2562  | 0.77546 |

Chloride Concentration in Gastric Contents

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 23328.25991 | 4665.65198  | 63.32   | 0.0001 |
| BALLOON(B)   | 1  | 9497.81333  | 9497.81333  | 128.89  | 0.0001 |
| DRUG         | 2  | 286.39699   | 143.19850   | 1.94    | 0.1449 |
| B*DRUG       | 2  | 2998.29542  | 1499.14771  | 20.34   | 0.0001 |
| HORSE*B*DRUG | 25 | 14493.94120 | 579.75765   | 7.87    | 0.0001 |
| TIME         | 11 | 1174.29352  | 106.75396   | 1.45    | 0.1497 |
| B*TIME       | 11 | 447.83056   | 40.71187    | 0.55    | 0.8663 |
| DRUG*TIME    | 22 | 2335.85801  | 106.17536   | 1.44    | 0.0926 |
| B*DRUG*TIME  | 22 | 2402.03069  | 109.18321   | 1.48    | 0.0771 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 540.394120  | 108.078824  | 1.47    | 0.2002 |
| post,t effect | 5  | 281.454861  | 56.290972   | 0.76    | 0.5764 |
| pre, b*t      | 5  | 311.874861  | 62.374972   | 0.85    | 0.5176 |
| post,b*t      | 5  | 111.588194  | 22.317639   | 0.30    | 0.9110 |
| pre,drug*t    | 10 | 829.902130  | 82.990213   | 1.13    | 0.3416 |
| post,drug*t   | 10 | 651.967778  | 65.196778   | 0.88    | 0.5477 |
| pre, b*drug*t | 10 | 753.623611  | 75.362361   | 1.02    | 0.4237 |
| post,b*drug*t | 10 | 578.434444  | 57.843444   | 0.78    | 0.6433 |

| Source        | DF | SS_N    | MS_N    | F Value | PValue  |
|---------------|----|---------|---------|---------|---------|
| pre, b effect | 1  | 4280.01 | 4280.01 | 13.0998 | 0.00102 |
| post,b effect | 1  | 5242.17 | 5242.17 | 16.0447 | 0.00035 |
| pre, d effect | 2  | 133.22  | 66.61   | 0.2039  | 0.81663 |
| post,d effect | 2  | 1007.17 | 503.58  | 1.5413  | 0.22971 |
| pre, d*b      | 2  | 3451.26 | 1725.63 | 5.2816  | 0.01047 |
| post, d*b     | 2  | 617.01  | 308.50  | 0.9442  | 0.39964 |

Chloride Output in Gastric Contents

| Source       | DF | Type I SS  | Mean Square | F Value | Pr > F |
|--------------|----|------------|-------------|---------|--------|
| HORSE        | 5  | 0.28817634 | 0.05763527  | 68.08   | 0.0001 |
| BALLOON(B)   | 1  | 0.55019419 | 0.55019419  | 649.89  | 0.0001 |
| DRUG         | 2  | 0.18821292 | 0.09410646  | 111.16  | 0.0001 |
| B*DRUG       | 2  | 0.02283793 | 0.01141897  | 13.49   | 0.0001 |
| HORSE*B*DRUG | 25 | 0.10821931 | 0.00432877  | 5.11    | 0.0001 |
| TIME         | 11 | 0.44263141 | 0.04023922  | 47.53   | 0.0001 |
| B*TIME       | 11 | 0.02301873 | 0.00209261  | 2.47    | 0.0055 |
| DRUG*TIME    | 22 | 0.16428786 | 0.00746763  | 8.82    | 0.0001 |
| B*DRUG*TIME  | 22 | 0.00970540 | 0.00044115  | 0.52    | 0.9650 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 0.04446698  | 0.00889340  | 10.50   | 0.0001 |
| post,t effect | 5  | 0.11751137  | 0.02350227  | 27.76   | 0.0001 |
| pre, b*t      | 5  | 0.00127950  | 0.00025590  | 0.30    | 0.9114 |
| post,b*t      | 5  | 0.01036171  | 0.00207234  | 2.45    | 0.0338 |
| pre,drug*t    | 10 | 0.00386552  | 0.00038655  | 0.46    | 0.9169 |
| post,drug*t   | 10 | 0.04230947  | 0.00423095  | 5.00    | 0.0001 |
| pre, b*drug*t | 10 | 0.00355522  | 0.00035552  | 0.42    | 0.9367 |
| post,b*drug*t | 10 | 0.00467181  | 0.00046718  | 0.55    | 0.8524 |

| Source        | DF | SS_N    | MS_N    | F Value | PValue  |
|---------------|----|---------|---------|---------|---------|
| pre, b effect | 1  | 0.20167 | 0.20167 | 77.933  | 0.00000 |
| post,b effect | 1  | 0.35991 | 0.35991 | 139.084 | 0.00000 |
| pre, d effect | 2  | 0.00493 | 0.00246 | 0.952   | 0.39547 |
| post,d effect | 2  | 0.30140 | 0.15070 | 58.237  | 0.00000 |
| pre, d*b      | 2  | 0.00727 | 0.00364 | 1.405   | 0.25854 |
| post, d*b     | 2  | 0.01704 | 0.00852 | 3.293   | 0.04872 |

Duodenal Content Volume

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 519376.657  | 103875.331  | 11.67   | 0.0001 |
| BALLOON(B)   | 1  | 3598900.231 | 3598900.231 | 404.20  | 0.0001 |
| DRUG         | 2  | 282222.977  | 141111.488  | 15.85   | 0.0001 |
| B*DRUG       | 2  | 589677.116  | 294838.558  | 33.11   | 0.0001 |
| HORSE*B*DRUG | 25 | 1404835.398 | 56193.416   | 6.31    | 0.0001 |
| TIME         | 11 | 322036.602  | 29276.055   | 3.29    | 0.0003 |
| B*TIME       | 11 | 191191.046  | 17381.004   | 1.95    | 0.0325 |
| DRUG*TIME    | 22 | 795468.634  | 36157.665   | 4.06    | 0.0001 |
| B*DRUG*TIME  | 22 | 392494.940  | 17840.679   | 2.00    | 0.0053 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 12611.148   | 2522.230    | 0.28    | 0.9221 |
| post,t effect | 5  | 106365.370  | 21273.074   | 2.39    | 0.0378 |
| pre, b*t      | 5  | 9242.093    | 1848.419    | 0.21    | 0.9592 |
| post,b*t      | 5  | 57847.833   | 11569.567   | 1.30    | 0.2637 |
| pre,drug*t    | 10 | 84652.324   | 8465.232    | 0.95    | 0.4867 |
| post,drug*t   | 10 | 39452.046   | 3945.205    | 0.44    | 0.9245 |
| pre, b*drug*t | 10 | 33904.713   | 3390.471    | 0.38    | 0.9546 |
| post,b*drug*t | 10 | 46453.139   | 4645.314    | 0.52    | 0.8747 |

| Source        | DF | SS_N       | MS_N       | F Value | PValue  |
|---------------|----|------------|------------|---------|---------|
| pre, b effect | 1  | 1193198.69 | 1193198.69 | 36.6589 | 0.00000 |
| post,b effect | 1  | 2529802.67 | 2529802.67 | 77.7238 | 0.00000 |
| pre, d effect | 2  | 82615.95   | 41307.98   | 1.2691  | 0.29425 |
| post,d effect | 2  | 870971.29  | 435485.64  | 13.3795 | 0.00005 |
| pre, d*b      | 2  | 29960.68   | 14980.34   | 0.4602  | 0.63506 |
| post, d*b     | 2  | 871853.53  | 435926.76  | 13.3931 | 0.00005 |

Bicarbonate Concentration in Duodenal Contents

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 3656.939286 | 731.387857  | 60.41   | 0.0001 |
| BALLOON(B)   | 1  | 2026.567940 | 2026.567940 | 167.39  | 0.0001 |
| DRUG         | 2  | 1257.839878 | 628.919939  | 51.95   | 0.0001 |
| B*DRUG       | 2  | 145.312574  | 72.656287   | 6.00    | 0.0028 |
| HORSE*B*DRUG | 25 | 5093.186650 | 203.727466  | 16.83   | 0.0001 |
| TIME         | 11 | 1050.913733 | 95.537612   | 7.89    | 0.0001 |
| B*TIME       | 11 | 146.883691  | 13.353063   | 1.10    | 0.3583 |
| DRUG*TIME    | 22 | 2725.646878 | 123.893040  | 10.23   | 0.0001 |
| B*DRUG*TIME  | 22 | 172.989442  | 7.863156    | 0.65    | 0.8860 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 62.627287   | 12.525457   | 1.03    | 0.3973 |
| post,t effect | 5  | 41.990059   | 8.398012    | 0.69    | 0.6286 |
| pre, b*t      | 5  | 71.945792   | 14.389158   | 1.19    | 0.3146 |
| post,b*t      | 5  | 70.392297   | 14.078459   | 1.16    | 0.3274 |
| pre,drug*t    | 10 | 189.799161  | 18.979916   | 1.57    | 0.1153 |
| post,drug*t   | 10 | 166.034097  | 16.603410   | 1.37    | 0.1925 |
| pre, b*drug*t | 10 | 81.233137   | 8.123314    | 0.67    | 0.7513 |
| post,b*drug*t | 10 | 76.908444   | 7.690844    | 0.64    | 0.7833 |

| Source        | DF | SS_N    | MS_N    | F Value | PValue  |
|---------------|----|---------|---------|---------|---------|
| pre, b effect | 1  | 1079.79 | 1079.79 | 10.1461 | 0.00353 |
| post,b effect | 1  | 1047.96 | 1047.96 | 9.8470  | 0.00397 |
| pre, d effect | 2  | 83.20   | 41.60   | 0.3909  | 0.68008 |
| post,d effect | 2  | 3558.25 | 1779.13 | 16.7172 | 0.00002 |
| pre, d*b      | 2  | 98.99   | 49.50   | 0.4651  | 0.63284 |
| post, d*b     | 2  | 47.05   | 23.52   | 0.2210  | 0.80307 |

Sodium Concentration in Duodenal Contents

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 7953.46635  | 1590.69327  | 18.51   | 0.0001 |
| BALLOON(B)   | 1  | 215.44566   | 215.44566   | 2.51    | 0.1143 |
| DRUG         | 2  | 8596.82849  | 4298.41425  | 50.03   | 0.0001 |
| B*DRUG       | 2  | 2849.44840  | 1424.72420  | 16.58   | 0.0001 |
| HORSE*B*DRUG | 25 | 29255.98279 | 1170.23931  | 13.62   | 0.0001 |
| TIME         | 11 | 488.42419   | 44.40220    | 0.52    | 0.8917 |
| B*TIME       | 11 | 1771.16769  | 161.01524   | 1.87    | 0.0421 |
| DRUG*TIME    | 22 | 1502.28611  | 68.28573    | 0.79    | 0.7322 |
| B*DRUG*TIME  | 22 | 1352.52704  | 61.47850    | 0.72    | 0.8235 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 198.754640  | 39.750928   | 0.46    | 0.8039 |
| post,t effect | 5  | 285.193595  | 57.038719   | 0.66    | 0.6512 |
| pre, b*t      | 5  | 195.668293  | 39.133659   | 0.46    | 0.8092 |
| post,b*t      | 5  | 438.983834  | 87.796767   | 1.02    | 0.4048 |
| pre,drug*t    | 10 | 763.087688  | 76.308769   | 0.89    | 0.5446 |
| post,drug*t   | 10 | 549.054734  | 54.905473   | 0.64    | 0.7800 |
| pre, b*drug*t | 10 | 877.234602  | 87.723460   | 1.02    | 0.4254 |
| post,b*drug*t | 10 | 468.155314  | 46.815531   | 0.54    | 0.8576 |

| Source        | DF | SS_N    | MS_N    | F Value | PValue  |
|---------------|----|---------|---------|---------|---------|
| pre, b effect | 1  | 1000.77 | 1000.77 | 1.60532 | 0.21529 |
| post,b effect | 1  | 220.51  | 220.51  | 0.35371 | 0.55666 |
| pre, d effect | 2  | 3754.18 | 1877.09 | 3.01099 | 0.06493 |
| post,d effect | 2  | 4256.85 | 2128.43 | 3.41416 | 0.04670 |
| pre, d*b      | 2  | 1257.56 | 628.78  | 1.00861 | 0.37724 |
| post, d*b     | 2  | 1352.38 | 676.19  | 1.08466 | 0.35142 |

Potassium Concentration in Duodenal Contents

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 20.55811758 | 4.11162352  | 40.00   | 0.0001 |
| BALLOON(B)   | 1  | 7.31931108  | 7.31931108  | 71.21   | 0.0001 |
| DRUG         | 2  | 8.98637101  | 4.49318551  | 43.71   | 0.0001 |
| B*DRUG       | 2  | 4.32570123  | 2.16285061  | 21.04   | 0.0001 |
| HORSE*B*DRUG | 25 | 38.71792471 | 1.54871699  | 15.07   | 0.0001 |
| TIME         | 11 | 10.50411559 | 0.95491960  | 9.29    | 0.0001 |
| B*TIME       | 11 | 1.60088225  | 0.14553475  | 1.42    | 0.1643 |
| DRUG*TIME    | 22 | 5.83152353  | 0.26506925  | 2.58    | 0.0002 |
| B*DRUG*TIME  | 22 | 1.54725131  | 0.07032960  | 0.68    | 0.8549 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 0.55986461  | 0.11197292  | 1.09    | 0.3662 |
| post,t effect | 5  | 2.00535033  | 0.40107007  | 3.90    | 0.0019 |
| pre, b*t      | 5  | 0.22016470  | 0.04403294  | 0.43    | 0.8288 |
| post,b*t      | 5  | 0.41056199  | 0.08211240  | 0.80    | 0.5512 |
| pre,drug*t    | 10 | 1.12691060  | 0.11269106  | 1.10    | 0.3644 |
| post,drug*t   | 10 | 0.85270776  | 0.08527078  | 0.83    | 0.6004 |
| pre, b*drug*t | 10 | 0.70248700  | 0.07024870  | 0.68    | 0.7398 |
| post,b*drug*t | 10 | 0.67188245  | 0.06718825  | 0.65    | 0.7670 |

| Source        | DF | SS_N    | MS_N    | F Value | PValue  |
|---------------|----|---------|---------|---------|---------|
| pre, b effect | 1  | 6.74506 | 6.74506 | 8.25450 | 0.00760 |
| post,b effect | 1  | 1.43206 | 1.43206 | 1.75254 | 0.19609 |
| pre, d effect | 2  | 2.76063 | 1.38031 | 1.68921 | 0.20266 |
| post,d effect | 2  | 9.11095 | 4.55547 | 5.57492 | 0.00906 |
| pre, d*b      | 2  | 1.55364 | 0.77682 | 0.95066 | 0.39842 |
| post, d*b     | 2  | 2.10887 | 1.05444 | 1.29040 | 0.29078 |

Chloride Concentration in Duodenal Contents

| Source       | DF | Type I SS   | Mean Square | F Value | Pr > F |
|--------------|----|-------------|-------------|---------|--------|
| HORSE        | 5  | 13649.48336 | 2729.89667  | 27.42   | 0.0001 |
| BALLOON (B)  | 1  | 638.45276   | 638.45276   | 6.41    | 0.0118 |
| DRUG         | 2  | 11923.06964 | 5961.53482  | 59.88   | 0.0001 |
| B*DRUG       | 2  | 3441.72173  | 1720.86086  | 17.28   | 0.0001 |
| HORSE*B*DRUG | 25 | 17811.55894 | 712.46236   | 7.16    | 0.0001 |
| TIME         | 11 | 2296.74541  | 208.79504   | 2.10    | 0.0203 |
| B*TIME       | 11 | 1781.89427  | 161.99039   | 1.63    | 0.0901 |
| DRUG*TIME    | 22 | 10931.68930 | 496.89497   | 4.99    | 0.0001 |
| B*DRUG*TIME  | 22 | 1390.41462  | 63.20066    | 0.63    | 0.8980 |

| Contrast      | DF | Contrast SS | Mean Square | F Value | Pr > F |
|---------------|----|-------------|-------------|---------|--------|
| pre,t effect  | 5  | 512.25045   | 102.45009   | 1.03    | 0.4005 |
| post,t effect | 5  | 426.80183   | 85.36037    | 0.86    | 0.5101 |
| pre, b*t      | 5  | 185.52497   | 37.10499    | 0.37    | 0.8672 |
| post,b*t      | 5  | 669.93027   | 133.98605   | 1.35    | 0.2448 |
| pre,drug*t    | 10 | 981.26528   | 98.12653    | 0.99    | 0.4558 |
| post,drug*t   | 10 | 1767.71427  | 176.77143   | 1.78    | 0.0643 |
| pre, b*drug*t | 10 | 712.42045   | 71.24205    | 0.72    | 0.7098 |
| post,b*drug*t | 10 | 380.28384   | 38.02838    | 0.38    | 0.9541 |

| Source        | DF | SS_N     | MS_N    | F Value | PValue  |
|---------------|----|----------|---------|---------|---------|
| pre, b effect | 1  | 1365.17  | 1365.17 | 3.4499  | 0.07229 |
| post,b effect | 1  | 14.35    | 14.35   | 0.0363  | 0.85013 |
| pre, d effect | 2  | 3905.72  | 1952.86 | 4.9351  | 0.01341 |
| post,d effect | 2  | 15066.50 | 7533.25 | 19.0373 | 0.00000 |
| pre, d*b      | 2  | 1398.75  | 699.38  | 1.7674  | 0.18672 |
| post, d*b     | 2  | 2354.94  | 1177.47 | 2.9756  | 0.06499 |

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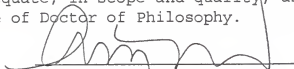
## BIOGRAPHICAL SKETCH

Diane L. Kitchen is the oldest of two children born to Hiram and Yvonne Kitchen. Born in Tacoma, Washington, she lived in several states before graduating from Lenoir City High School in 1977. She spent a year in England as an AFS exchange student where she completed her "A level" exams before returning to the States to enter the University of Tennessee in Knoxville. During her studies there, she was elected into the Alpha Zeta, Phi Zeta and Phi Kappa Phi honorary fraternities. After finishing undergraduate requirements, Diane returned to England to work in a veterinary practice until her admission to the College of Veterinary Medicine. She received her Doctor of Veterinary Medicine from the University of Tennessee in 1984.

During an internship and residency in Large Animal Internal Medicine at Texas A & M University, Diane received the Waddell Scholarship Award for excellence in emergency and intensive care. In 1990, she passed her qualifying examination for the American College of Veterinary Internal

Medicine. Diane began a solo large animal private practice in Marion County, Florida, in 1989. She has served on the executive committee for the Marion Veterinary Medical Association since 1992 and was the president during 1996. She is also an active member of the American Veterinary Medical Association and Florida Cattleman Association.

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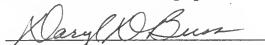
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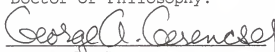
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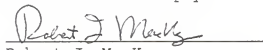


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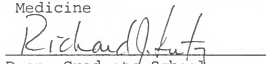
  
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Robert J. MacKay  
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This dissertation was submitted to the Graduate Faculty of the College of Veterinary Medicine and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

May, 1997

  
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